DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE
WASHINGTON DC

DODI3216.02_AFI40-402_AFGM2021-01

16 July 2021

MEMORANDUM FOR DISTRIBUTION C
MAJCOMs/FOAs/DRUs

FROM: AF/SG

SUBJECT: Air Force Guidance Memorandum to DODI3216.02_AFI40-402, *Protection of Human Subjects and Adherence to Ethical Standards in Air Force Supported Research*

By Order of the Secretary of the Air Force, this Air Force Guidance Memorandum (AFGM) immediately implements changes to DODI3216.02_AFI40-402. This AFGM reissues the attachment to DODI3216.02_AFI40-402_AFGM2020-01 with no changes. Compliance with this AFGM is mandatory. To the extent its directions are inconsistent with other Air Force publications, the information herein prevails, in accordance with DAFI 33-360, *Publications and Forms Management*.

The intent of the changes described in this AFGM is to standardize the Air Force's review requirements with the other Military Services and within the Department of Defense; replace existing requirements with alternative approaches that are less burdensome for investigators and research oversight officials; and clarify unclear statements. This will assist in decreasing the amount of time needed to get research studies approved.

This AFGM becomes void after one year has elapsed from 15 July 2021, or upon incorporation by interim change to, or rewrite of DODI3216.02_AFI40-402, whichever is earlier**.**

ROBERT I. MILLER
Lieutenant General, USAF, MC, SFS
Surgeon General

Attachment:
Changes to DODI3216.02_AFI40-402

(Revise) Enc 1, Reference (s) “DoDI 6025.18, “Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule Compliance In DoD Health Care Programs”, March 13, 2019 and DoDM 6025.18, “Implementation of the Health Insurance Portability And Accountability Act (HIPAA) Privacy Rule in DoD Health Care Programs”

(Revise) Enc 2, Sec 4.g “(Added)(AF) Provide subject matter expertise to support AFMRA/SGE-C’s review of research involving human subjects by supporting the use of AF/SG consultants, as necessary.”

(Revise) Enc 2, Sec 5.c. “(Added)(AF) Maintain adequate staffing consisting of personnel with appropriate human research protection expertise; consults with AF/SG consultants as necessary to obtain expertise in other areas (e.g., medical, social-cultural, and operational) for review of activities that may include research involving human subjects.”

(Revise) Enc 2, Sec 6(l) “(Added)(AF) Establish procedures for ensuring investigators obtain prior written permission from institutional leadership to target for participation in research that institution’s subject populations (e.g., their personnel, patients, and/or identifiable private information about such persons), prior to allowing access. Researchers shall follow each institution’s policies regarding the requirement to obtain command permission. If the institution does not have such policies, researchers will obtain permission from an institutional leader with responsibility over the subject population sought. In determining whether to permit the research, these supporting institutions should consider local mission requirements (e.g., would participation affect personnel ability to mobilize for readiness, to perform duties, or to be available for duty). (T-0: OUSD(R&E) approved policy)”

(Revise) Enc 2, Sec 8(h) “(Added)(AF) Submit to AFMRA/SGE-C, prior to start, all research described under subparagraph 3.b.(1) of Enclosure 3. Submit to AFMRA/SGE-C, as requested, a table listing all non-exempt IRB approved protocols not requiring prior review per subparagraph 3.b.(1) of Enclosure 3 and all dates of IRB meetings conducted since the last report. Upon request, each IRB will submit to AFMRA/SGE-C a copy of a selected IRB-approved protocol, to include IRB approval notice and final approved versions of components of the protocol or a copy of a set of IRB meeting minutes. SGE-C will conduct a compliance review per paragraph 5.j. of Enclosure 2 and coordinate resolution of any compliance issues raised upon audit of the IRB review of the protocol submission or set of IRB meeting minutes.”

(Revise) Enc 2, Sec 9(i) “(Added)(AF) Submit to AFMRA/SGE-C, as requested, a table listing all research HRPO reviewed and issued a final HRPO determination. Upon request, each HRPO will submit to AFMRA/SGE-C a copy of a selected HRPO-approved protocol to include HRPO determination letter and support documentation. SGE-C will conduct a compliance review per paragraph 5.j. of this enclosure and coordinate resolution of any compliance issues raised upon audit of the HRPO review. Submit to AFMRA/SGE-C for final coordination any research involving human subjects that requires ASD(R&E) approval prior to start.”

(Revise) Enc 2, Sec 10.d “(Added)(AF) Review activities that may include research involving human subjects per section 219.102 of Reference (c) to determine whether they are:”

(Revise) Enc 2, Sec 10.d(1) “Activities that are not research involving human subjects per section 219.102 of Reference (c)”

(Revise) Enc 3, Sec 3a(1)(a) "(Added)(AF) AF authorizes only AFMRA/SGE-C, IRBs, and EDOs to make official determinations per sections 219.101(b) and 102 of Reference (c) for AF conducted activities that may include research involving human subjects per section 219.102 of Reference (c)."

(Revise) Enc 3, Sec 3a(1)(b) "(Added)(AF) For AF-conducted collaborative activities involving other DoD Components that may include research involving human subjects per section 219.102 of Reference (c), other DoD Component research review authorities per the collaborating DoD Component instruction may also make official determinations per sections 219.101(b) and 102 of Reference (c)."

(Delete) Enc 3, Sec 3b(1)(f) "(Added)(AF) The research has been determined by an AF IRB to involve greater than minimal risk to subjects. (T-0: OUSD(R&E) approved policy)"

(Delete) Enc 3, Sec 3b(1)(f)1 "NCI's NCTN activity approved by an AF IRB are excepted from the requirement for AFMRA/SGE-C review and approval prior to start. Instead, they will be submitted to AFMRA/SGE-C for potential audit, per paragraph 5.j. of Enclosure 2."

(Delete) Enc 3, Sec 3b(1)(g) "(Added)(AF) The research is a NCTN activity and the engaged DoD institution is relying upon the NCI's CIRB. See paragraph 3.a.(8)(a)1 of this Enclosure."

(Revise and renumber) Enc 3, Sec 3b(1)(h) "(Added)(AF) The research involves biological or chemical warfare agents or weapons and is not prohibited by 50 U.S.C. 1520a. (T-0: OUSD(R&E) approved policy)" to Enc 3, Sec 3b(1)(f).

(Revise and renumber) Enc 3, Sec 3b(1)(i) "(Added)(AF) The activity is either exempt (per section 219.101(b) of Reference (c)) or non-exempt research involving human subjects, and involves collection of statistical information under a promise of confidentiality per the Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA) and section 512 of Public Law 107-347 (Reference (k). Submit this research to AFMRA/SGE-C with documentation of approval of SAF/CIO A6. (T-0: OUSD(R&E) approved policy)" to Enc 3, Sec 3b(1)(g).

(Delete) Enc 3, Sec 3b(1)(j) "(Added)(AF) The research involves an FDA regulated investigational drug or investigational device. (T-0: OUSD(R&E) approved policy,)"

(Delete) Enc 3, Sec 3b(1)(k) "(Added)(AF) A proposed substantive change to approved research makes it fall within a category requiring AFMRA/SGE-C approval prior to start per subparagraph 3.b.(1) of this enclosure. (T-0: OUSD(R&E) approved policy)"

(Revise) Enc 3, Sec 4b(1)(a) "(Added)(AF) Successful completion of HRPO review is required prior to initiation of AF supported research involving human subjects. Submit all required paperwork for contracts, grants, and other awards to enable HRPO review (see paragraph 4.c. of Enclosure 3). The non-DoD institution shall ensure receipt of confirmation that the HRPO review is complete and that the activity is compliant prior to initiation of the research. (T-0: OUSD(R&E) approved policy)"

(Revise) Enc 3, Sec 4b(1)(b) "(Added)(AF) Provide to the HRPO written documentation of IO/AIO approval from each engaged DoD institution along with leadership permission from each institution that is providing support to the research (e.g., via provision of facilities, equipment, or personnel). (T-0: Paragraphs 6.a.(2) of Enclosure 2, and 6.l.)"

(Delete) Enc 3, Section 4c(7) "(Added)(AF) AFMRA/SGE-C administrative review and approval is required prior to start of any category of non-DoD conducted activities approved by an AF IRB identified in section 3.b.1. of Enclosure 3. (T-0: OUSD(R&E) approved policy)"

(Delete) GLOSSARY Part I. Abbreviations and Acronyms "(Added)(AF) SGHARP AF/SG's Human and Animal Research Panel"

(Revise) GLOSSARY PART II. DEFINITIONS. "(Added)(AF) EDO. Serves as an AF HRPP official delegated authority by the IO/AIO and AFMRA/SGE-C to ensure compliance of the AF institution's proposed activities with human subjects prior to initiation per section 10 of Enclosure 2."

(Replace) GLOSSARY PART II. DEFINITIONS. Change to "Part II. Definitions."

(Delete) GLOSSARY Part II. Definitions "(Added)(AF) SGHARP. A panel of experts appointed to routinely provide advice to AFMRA/SGE-C regarding the most ethically and/or scientifically challenging research involving human subjects and/or animal use under AFMRA/SGE-C review per sections 3 and 4 of Enclosure 3."

BY ORDER OF THE
SECRETARY OF THE AIR FORCE

DODI3216.02_AFI40-402

10 SEPTEMBER 2014

Medical Command

PROTECTION OF HUMAN SUBJECTS AND ADHERENCE TO ETHICAL STANDARDS IN AIR FORCE SUPPORTED RESEARCH

COMPLIANCE WITH THIS PUBLICATION IS MANDATORY

ACCESSIBILITY: **Publications and forms are available on the e-Publishing website at www.e-publishing.af.mil for downloading or ordering.**

RELEASABILITY: **There are no releasability restrictions on this publication.**

OPR: AFMSA/SGE-C

Certified by: AFMSA (Brig Gen James McClain, USAF)

Supersedes: AFI40-402, 5 March 2005

Pages: 60

This supplement implements and extends the instructions of Department of Defense (DoD) Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research, November 8, 2011. The DoD Instruction (DoDI) is printed word-for-word in regular font, without editorial review. Air Force supplementary material is printed in bold font and indicated by "(Added)(AF)." This supplement replaces AFI 40-402. This supplement describes Air Force responsibilities under the instruction and establishes the Air Force requirement to support the program. This supplement applies to all Air Force activities and the Air Force component of the Air National Guard and the Air Force Reserve. Ensure that all records created as a result of processes prescribed in this publication are maintained in accordance with Air Force Manual (AFMAN) 33-363, Management of Records, and disposed of in accordance with Air Force Records Information Management System (AFRIMS) Records Disposition Schedule (RDS). Refer recommended changes and questions about this publication to the Office of Primary Responsibility (OPR) using the AF Form 847, Recommendation for Change of Publication; route AF Forms 847 from the field through the appropriate functional chain of command. This publication may be supplemented at any level, but all direct supplements must be routed to the OPR of this publication for coordination prior to certification and approval.

The authorities to waive wing/unit level requirements in this publication are identified herein, e.g., with a Tier ("T-0, T-1") number following the compliance statement. See AFI 33-360, Publications and Forms Management, for a description of the authorities associated with the Tier numbers.

Submit requests for waivers through the chain of command to the appropriate Tier waiver approval authority, or alternately, to the Publication OPR for non-tiered compliance items.

SUMMARY OF CHANGES

This document has been substantially revised and must be completely reviewed. Major changes include: updates OPR office symbol from AFMSA/SGRC to AFMSA/SGE-C; updates OPR office symbol for the purposes of Reference (v) from AFMSA/SGRC to AFMSA/SG5I; deletes the Surgeon General's Research Oversight Committee, a voting authority and substitutes the Surgeon General's Human and Animal Research Panel (SGHARP), an advisory body; deletes the requirement for specific Commands to maintain Clinical Investigation Facilities or Institutional Review Boards (IRBs); clarifies that Institutional Official/Authorized Institutional Official (IO/AIO) approval of research prior to start is a requirement, but not the responsibility of the IRB; adds procedures to discourage requiring duplicate IRB reviews; updates assurance requirements; clarifies requirements for the Research Oversight and Compliance Division (AFMSA/SGE-C) and Human Research Protection Official (HRPO) review of research; allows AFMSA/SGE-C to delegate HRPO authority; updates human research protection education training requirements.

Department of Defense
INSTRUCTION

NUMBER 3216.02
November 8, 2011

USD(AT&L)

SUBJECT: Protection of Human Subjects and Adherence to Ethical Standards in ~~DoD~~ **Air Force** Supported Research

References: See Enclosure

1. PURPOSE. This Instruction reissues DoD Directive (DoDD) 3216.02 (Reference (a)) as a DoD Instruction in accordance with the authority in DoDD 5134.01 (Reference (b)) to establish policy and assign responsibilities for the protection of human subjects in DoD-supported programs to implement part 219 of title 32, Code of Federal Regulations (CFR) (also known and hereinafter referred to as "the Common Rule" (Reference (c)). **DoD text appears in regular font and Air Force text appears in bold font in accordance with AFI 33-360.**

2. APPLICABILITY

a. This Instruction applies to:

(1) OSD, the Military Departments, the Office of the Chairman of the Joint Chiefs of Staff and the Joint Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities, and all other organizational entities within the Department of Defense (hereinafter referred to collectively as the "DoD Components").

(a) (Added)(AF) This instruction applies to the U. S. Air Force (AF), which, for the purposes of this Instruction, includes the Air Reserves Components (encompassing the Air National Guard and Air Force Reserve).

(2) All DoD-conducted or -supported research involving human subjects as defined in the Glossary. All such activities must include both systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or about whom identifiable private information is obtained. All activities meeting both of these conditions will hereinafter be referred to as "research involving human subjects" in this Instruction.

(3) Activities such as research, development, testing, and evaluation (RDT&E) that meet the definition of research involving human subjects (as defined in the Glossary), as well as clinical investigations or medical activities regulated by the Food and Drug Administration (FDA) in parts 50, 56, 312, 600, and 812 of title 21, CFR (Reference (d)).

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

3. DEFINITIONS. See Glossary.

4. POLICY. It is DoD policy that:

a. All research involving human subjects that is conducted or supported by the Department of Defense shall comply with part 219 of Reference (c), which incorporates the ethical principles of respect for persons, beneficence, and justice, as codified in page 23192 of the Federal Register (also known as "The Belmont Report" (Reference (e)).

b. Certain categories of human subjects in research are recognized as vulnerable populations, groups, or individuals and are afforded additional protections as specified in section 7 of Enclosure 3 of this Instruction.

c. Research involving human subjects for testing of chemical or biological warfare agents is generally prohibited by section 1520a of title 50, United States Code (U.S.C.) (Reference (f)), subject to possible exceptions for research for prophylactic, protective, or other peaceful purposes.

d. DoD-appropriated funds shall not be used to support research involving a human being as an experimental subject, as defined in this Instruction, without the prior informed consent of the experimental subject or in accordance with section 980 of title 10, U.S.C. (Reference (g)) and this Instruction (see section 9 of Enclosure 3 of this Instruction for details). The definitions of research involving a human being as an experimental subject and research involving human subjects are different; see the Glossary for an explanation.

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

5. RESPONSIBILITIES. See Enclosure 2.

6. PROCEDURES. See Enclosure 3.

7. RELEASABILITY. UNLIMITED. This Instruction is approved for public release and is available on the Internet from the DoD Issuances Website at http://www.dtic.mil/whs/directives.

8. EFFECTIVE DATE. This Instruction is effective upon its publication to the DoD Issuances Website.

Frank Kendall
Acting
Under Secretary of Defense for Acquisition, Technology and Logistics

THOMAS W. TRAVIS, Lieutenant General
USAF, MC, CFS
Surgeon General

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ENCLOSURE 1

REFERENCES

(a) DoD Directive 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," March 25, 2002 (hereby cancelled)
(b) DoD Directive 5134.01, "Under Secretary of Defense for Acquisition, Technology and Logistics (USD(AT&L))," December 9, 2005
(c) Parts 22 (Appendix B), 37 (Appendix D), 108 and 219[1] of title 32, Code of Federal Regulations
(d) Parts 50, 56, 312, 600, and 812 of title 21, Code of Federal Regulations
(e) Page 23192 of Volume 44, Federal Register, April 18, 1979 (also known as "The Belmont Report") [2]
(f) Section 1520a of title 50, United States Code
(g) Sections 139(a)(2)(A), 980, 1074f , and 1102 of title 10, United States Code
(h) Part 46, subparts A-D of title 45, Code of Federal Regulations
(i) Memorandum of Understanding between the Food and Drug Administration and the Department of Defense, "Concerning Investigational Use of Drugs, Antibiotics, Biologics, and Medical Devices by the Department of Defense," May 21, 1987
(j) Sections 241(d) and 289g–289g-2 of title 42, United States Code
(k) Public Law 107-347, "Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA)," December 17, 2002
(l) Pages 33362-33377 of Volume 72, Federal Register, June 15, 2007
(m) Sections 2105, 3109, 3371-3376,[3] and 5536 of title 5, United States Code
(n) Sections 2.101 and 252.235-7004 of title 48, Code of Federal Regulations
(o) Section 252 of Public Law 103-160, "National Defense Authorization Act for Fiscal Year 1994," November 30, 1993
(p) DoD Directive 2310.01E, "The Department of Defense Detainee Program," September 5, 2006
(q) Section 30 of title 24, United States Code
(r) Executive Order 13526, "Classified National Security Information," December 29, 2009
(s) DoD 6025.18-R, "DoD Health Information Privacy," January 24, 2003
(t) Executive Order 12333, "United States Intelligence Activities," as amended, August 18, 2010
(u) DoD 5400.11-R, "Department of Defense Privacy Program," May 14, 2007
(v) ~~DoDI 6000.08, "Funding and Administration of Clinical Investigation Programs," December 3, 2007~~ **(Added)(AF) DoD Instruction 6000.08, "Defense Health Program Research and Clinical Investigation Programs," January 22, 2014**
(w) DoD Instruction 5025.01, "DoD Directives Program," October 28, 2007

[1] Also known as "the Common Rule"
[2] Available on the Internet at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm. The Belmont Report's 2-volume appendix is available from the Government Printing Office as DHEW Publication Nos. (OS) 78-0013 and (OS) 78-0014
[3] Also known as "The Intergovernmental Personnel Act of 1970, as amended"

(x) DoD Instruction 6200.02, “Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Program,” February 27, 2008
(y) DoD Instruction 6025.13, “Medical Quality Assurance (MQA) and Clinical Quality Management in the Military Health System (MHS),” February 17, 2011
(z) DoD Directive 5240.01, “DoD Intelligence Activities,” August 27, 2007
(aa) (Added)(AF) AFI 40-402, “Protection of Human Subjects In Research”, 5 May 2005 (hereby cancelled)
(bb) (Added)(AF) DoDI 3210.07, “Research Integrity and Misconduct”, 14 May 2004
(cc) (Added)(AF) AFPD 40-4, “Clinical Investigation and Human Use in Medical Research”, 11 May 1994
(dd) (Added)(AF) AFI 38-501, “Air Force Survey Program”, 12 May 2010
(ee) (Added)(AF) AFI 33-324, “The Information Collections and Reports Management Program; Controlling Internal, Public, and Interagency Air Force Information Collections”, 1 June 2000
(ff) (Added)(AF) 45 Comptroller General 649
(gg) (Added)(AF) DoDI 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*

ENCLOSURE 2

RESPONSIBILITIES

1. ASD(R&E). The ASD(R&E), under the authority, direction, and control of the Under Secretary of Defense for Acquisition, Technology, and Logistics, shall:

a. Be the single DoD point of contact for all matters related to DoD compliance with this Instruction and shall act as the principal DoD liaison with organizations outside the Department of Defense on matters pertaining to research involving human subjects.

b. Provide guidance and procedures necessary to implement this Instruction. The ASD(R&E) will consult with the Assistant Secretary of Defense for Health Affairs (ASD(HA)) for matters affecting medical research involving human subjects.

c. Exercise the authorities of the Head of the Department identified in part 219 of Reference (c), the Secretary as identified in subparts B-D of part 46 of title 45, CFR (Reference (h)) for research described in section 7 of Enclosure 3 of this Instruction, and the Secretary of Defense identified in section 980 of Reference (g).

d. Grant exceptions to any procedures or requirements in this Instruction based upon an appropriate justification from the Head of an OSD or DoD Component and consistent with law.

e. Establish a process to oversee the DoD Components' implementation of their respective Component human research protection program (HRPP) management plan and compliance with this Instruction.

f. Establish a framework for educational training requirements for DoD personnel in key HRPP roles commensurate with their duties and responsibilities.

g. Work with the DoD Components supporting international research involving human subjects to resolve conflicts between this Instruction, including its references, and other applicable foreign laws and requirements.

(1) (Added)(AF) Submit to AFMSA/SGE-C, for final determination, conflicts between applicable U. S. requirements and international requirements in AF supported or conducted research involving human subjects, with appropriate analysis and recommendations.

h. Maintain a list of foreign country and international standards that are at least equivalent to those in part 219 of Reference (c).

i. Designate DoD representatives to Federal committees, such as the Human Subject Research Subcommittee of the National Science and Technology Council's Committee on Science or other committees established by the White House.

j. Designate a DoD representative to the Secretary's Advisory Committee on Human Research Protection established by the Secretary of Health and Human Services (HHS) and successor entities established by the Secretary of HHS.

k. Establish the DoD Coordinating Committee for Human Research Protection Programs (CCHRPP) to act as the central advisory committee to the ASD(R&E) on all matters regarding the ethical involvement of human subjects in research. Membership shall be appointed as described in section 18 of Enclosure 3 of this Instruction.

2. ASD(HA). The ASD(HA), under the authority, direction, and control of the Under Secretary of Defense for Personnel and Readiness (USD(P&R)), shall:

a. Advise the ASD(R&E) on matters related to the participation of human subjects in research, especially regarding medical safety, bioethics, and standards of professional health care and conduct.

b. Represent the Department of Defense on matters relating to implementation of FDA regulatory requirements in Reference (d) and the Memorandum of Understanding between the FDA and the Department of Defense (Reference (i)).

3. HEADS OF THE OSD AND DoD COMPONENTS. The Heads of the OSD and DoD Components that conduct or support research involving human subjects covered by this Instruction shall:

a. Develop, issue, and monitor a Component HRPP management plan (see section 1 of Enclosure 3 of this Instruction for details).

b. Establish and oversee DoD Component policies and procedures that ensure compliance with this Instruction and any other supplementing or implementing issuances (see section 1 of Enclosure 3 for details).

c. Exercise the authority as outlined in this Instruction.

d. Oversee each institutional official's (IO) (see Glossary) implementation of their organization's HRPP.

e. Provide members to intra- and interagency committees and to the CCHRPP when requested by the ASD(R&E) consistent with section 18 of Enclosure 3.

f. Provide in a timely manner to the ASD(R&E) the following:

(1) A copy of all reports provided to the appropriate Congressional Committees in accordance with Reference (f) for any research involving human subjects for testing of chemical

or biological warfare agents. DoD Components shall also send a copy to the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs.

(2) Copies of any waivers from requirements that have been granted in accordance with this Instruction.

(3) Copies of any approved fetal research covered under sections 289g–289g-2 of title 42, U.S.C. (Reference (j)).

(4) Copies of any research involving human subjects conducted consistent with section 512 of Public Law 107-347 (Reference (k)). DoD Components shall also send a copy to the Office of Management and Budget (OMB), as required by Reference (k) and pages 33362-33377 of Volume 72, Federal Register (Reference (l)).

(5) Any allegation of serious or continuing noncompliance related to research involving human subjects that has been substantiated by inquiry or investigation and any subsequent actions taken based on the findings consistent with section 16 of Enclosure 3. The DoD Component may send an initial notification of potential serious or continuing noncompliance to ASD(R&E) based on the gravity or magnitude of the initial allegation.

(6) Any notifications to a DoD Component by another Federal agency or by an appropriate State agency or foreign government that an institution of the Component is under investigation for cause or for noncompliance with the applicable laws and regulations, including the Common Rule.

(7) Any substantiated unanticipated problems involving risks to human subjects or others (UPIRTSO).

g. Maintain all records identified in this Instruction or required by a reference in this Instruction as described in section 15 of Enclosure 3.

4. (Added)(AF) AF SURGEON GENERAL (AF/SG). The AF/SG, under the authority of the Secretary of the AF, shall:

a. (Added)(AF) For the purposes of AF compliance with this Supplement, the Head of the DoD Component is AF/SG. AF/SG is the single point of authority for AF compliance with this Instruction and shall act as the principal AF liaison with other DoD Components on matters pertaining to AF research involving human subjects. This authority has been delegated to AFMSA/SGE-C and cannot be further delegated.

b. (Added)(AF) Establish and properly resource the AF HRPP, including AFMSA/SGE-C, to ensure the protection and welfare of human subjects in research supported or conducted by the AF.

c. (Added)(AF) Ensure AFMSA/SGE-C forwards to ASD(R&E) all items identified in subparagraph 3.f. of this enclosure.

d. (Added)(AF) Forward to the Secretary of Defense via ASD(R&E) all classified human subject research for approval.

e. (Added)(AF) Develop, issue, and monitor an AF HRPP management plan.

f. (Added)(AF) Establish and oversee AF policies and procedures that ensure compliance with Federal, DoD and AF requirements.

g. (Added)(AF) Provide subject matter expertise to support AFMSA/SGE-C's review of research involving human subjects by appointing a Surgeon General's Human and Animal Research Panel (SGHARP) and supporting use of AF/SG consultants, as necessary.

h. (Added)(AF) Oversee each AF IO's implementation of their institution's HRPP.

i. (Added)(AF) Appoint and provide members to intra- and interagency committees and to the CCHRPP when requested by the ASD(R&E) per section 18 of Enclosure 3.

j. (Added)(AF) Provide blanket authorization for AF participation in the National Cancer Institute's (NCI) Clinical Trials Cooperative Group Program.

k. (Added)(AF) Serve as the final authority on implementation of Reference (bb) for research misconduct involving human subjects. May exercise authorities that otherwise would be delegated to AF institutions.

5. (Added)(AF) <u>RESEARCH OVERSIGHT AND COMPLIANCE (AFMSA/SGE-C).</u> AFMSA/SGE-C, under the authority of the AF/SG, shall:

a. (Added)(AF) Serve as the DoD Component office referenced herein for the AF HRPP. Provide support and expertise to the AF HRPP for research involving human subjects conducted or supported by the AF. Coordinate policy and interpret regulations for the HRPP. Issue routine guidance, and procedures (e.g., handbooks and templates).

b. (Added)(AF) Manage the AF HRPP by overseeing its implementation and operation.

c. (Added)(AF) Maintain adequate staffing consisting of personnel with appropriate human research protection expertise; consults with the SGHARP and AF/SG consultants as necessary to obtain expertise in other areas (e.g., medical, social-cultural, and operational) for review of activities that may include research involving human subjects.

d. (Added)(AF) Manage and oversee review and processing of HRPP documentation.

(1) (Added)(AF) Prior to permitting engagement in non-exempt research involving human subjects and after ensuring compliance, approve DoD assurances and HRPPs (and, prior to initiation, substantive changes thereto) for AF institutions. Accept DoD assurances

issued by other DoD Components. Accept Federal (non-DoD) assurances deemed appropriate for the research.

(2) (Added)(AF) May suspend or terminate DoD assurances, Individual Investigator Agreements (IIAs), and/or Institutional Agreements for IRB Review (IAIRs) as necessary to ensure protection of human subjects in research, or in cases of serious or continuing non-compliance.

e. (Added)(AF) Establish a process for and perform administrative review and approval of DoD conducted research per section 3 of Enclosure 3 prior to initiation. May suspend or terminate such research as necessary to ensure protection of human subjects.

f. (Added)(AF) Establish a process for and perform HRPO review and determination on non-DoD conducted research per section 4 of Enclosure 3 prior to initiation.

(1) (Added)(AF) May suspend or terminate such research as necessary to ensure protection of human subjects.

(2) (Added)(AF) May delegate HRPO authority to AF personnel with appropriate training and expertise as needed. See section 9 of this enclosure.

g. (Added)(AF) Perform functions as delegated by the AF/SG or through the AF Management Plan.

h. (Added)(AF) Has authority to provide Exempt Determination Official (EDO) support, as necessary, as described in paragraph 10.d. of this enclosure.

i. (Added)(AF) Support AF institutions in establishing and maintaining HRPPs, obtaining DoD assurances, and establishing IRBs.

j. (Added)(AF) Oversee and monitor the AF HRPP via implementation of a quality assurance review program to ensure appropriate compliance oversight over each AF institution's HRPP. This program shall include site visits to AF HRPPs with internal IRBs, random and/or for cause audits of AF IRB, EDO, HRPO and AFMSA/SGE-C determinations, and audit of AF IRB minutes. Provide feedback to AF institutions' HRPP personnel regarding recommendations for improvement and deficiencies requiring resolution; review proposed corrective action plans to address any deficiencies.

k. (Added)(AF) Establish initial and ongoing role-based HRPP education and training for AF personnel and issue training guidance, consistent with the standards set forth by ASD(R&E) per section 5 of Enclosure 3.

l. (Added)(AF) Ensure allegations of UPIRTSOs and serious or continuing non-compliance are appropriately investigated, substantiated, and addressed by institutions and reported to ASD(R&E), as required per paragraph 5.p. of this enclosure.

m. (Added)(AF) Ensure the following events occurring in AF supported or conducted research that require reporting to the FDA per Reference (d) are appropriately investigated and addressed: adverse events associated with use of drugs (see 21 CFR 312), adverse experiences associated with use of biologics (see 21 CFR 600), or unanticipated adverse device effects (see 21 CFR 812).

n. (Added)(AF) Investigate allegations of research misconduct involving human subjects, in lieu of local institutional review, if appropriate, per paragraph 16.b. of Enclosure 3.

o. (Added)(AF) Maintain records regarding the AF HRPP as required, e.g., AFMSA/SGE-C determinations and reports submitted per paragraph 3.f. of this enclosure.

p. (Added)(AF) Channel to higher-level authorities (e.g., by AF/SG, ASD(R&E), or the Secretary of Defense) all AF supported activities requiring their review. AFMSA/SGE-C shall also:

(1) (Added)(AF) Forward to ASD(R&E) all items required by paragraph 3.f. of this enclosure.

(2) (Added)(AF) Prepare reports for higher level officials, as needed.

(3) (Added)(AF) Review to confirm compliance, after the IRB deems compliant, any request for a waiver, exception, and/or approval of items requiring higher-level review.

~~4.~~6 IOs OF DoD INSTITUTIONS. Each IO, under the authority, direction, and control of the Heads of the OSD and DoD Components shall:

a. Establish and maintain an HRPP to ensure the institution's compliance with this Instruction.

(1) (Added)(AF) AF institutions shall obtain approval of their HRPP from AFMSA/SGE-C prior to implementation. (T-0: Paragraph 3.a.(5) of Enclosure 3)

(a) (Added) AF) Institutions can obtain HRPP templates from AFMSA/SGE-C or may write their own HRPPs. The HRPP identifies policies and procedures to ensure compliance and protection of human subjects in research. Compliant HRPPs:

1. (Added)(AF) Designate one or more EDOs and/or IRBs, as appropriate, to review for compliance, before initiation, the institution's activities that are, or may be, research involving human subjects. Describe processes to ensure any individual designated authority to determine research or exempt status does so in accordance with procedures documented in the HRPP. (T-0: Paragraph 2.a.(3) of Enclosure 3)

2. (Added)(AF) Describe policies and procedures for auditing the institution's HRPP records, i.e., any research involving human subjects either supported by the institution or reviewed by the institution's IRB. See paragraph 7.g. of this enclosure.

(2) (Added)(AF) Establish procedures for review and approval of each study by the IO, AIO, or other senior institutional official before the institution becomes engaged in research involving human subjects and prior to initiation of any substantive changes thereto. The purpose of this review is to determine, on behalf of the institution and in light of local mission considerations, whether to permit the research. This review can be done before or after IRB approval, and is not part of the IRB review process.

(3) (Added)(AF) Include policies and procedures to suspend or terminate IRB approval of research when necessary to ensure protection of human subjects. (T-0: Paragraph 2.a.(3) of Enclosure 3)

(4) (Added)(AF) Include policies and procedures for review of allegations of research misconduct. (T-0: Reference (bb))

(5) (Added)(AF) Include policies and procedures for reporting and review of allegations of serious or continuing noncompliance, and UPIRTSOs, to include review by an appropriate office (e.g., the IRB, if applicable), assessment of corrective action, and creation of a written report regarding the events and the reviewing office's findings. Include the same for any of the following events occurring in research conducted or supported by the institution, and that require reporting to the FDA per Reference (d): adverse events associated with the use of drugs (see 21 CFR 312), adverse experiences associated with the use of biologics (see 21 CFR 6000), or unanticipated adverse device effects (see 21 CFR 812). (T-0: Id)

(6) (Added)(AF) Facilitate collaborative research involving human subjects by eliminating or minimizing duplication of required reviews, when possible. Include policies, procedures, and training to reduce the number of reviews (IRB and administrative) that occur in DoD-conducted collaborative research (see definition of "intramural research", in Part II herein). Multiple HRPP reviews not required by this instruction should not be conducted without written justification to, and concurrence from, AFMSA/SGE-C. (T-0: Paragraph 1.c.(4) of Enclosure 3)

(7) (Added)(AF) Include policies and procedures requiring identification and disclosure of conflicts of interest, not limited to financial. (T-0: Paragraph 1.c.(7) of Enclosure 3)

b. Provide the resources needed to ensure compliance with this Instruction.

(1) (Added)(AF) The IO will support any IRBs used to ensure the institution's compliance. (T-0: Section 219.103 of Reference (c))

(a) (Added)(AF) For IRBs established as part of the institution, the IO shall:

1. (Added)(AF) Approve IRB membership. To ensure there is no appearance of undue influence, an IO/AIO should not be members of their institution's IRB.

2. (Added)(AF) Report to AFMSA/SGE-C changes to the roster(s) of any IRBs that are part of the institution on a quarterly basis.

3. (Added)(AF) Ensure the IRB considers the scientific review of all non-exempt research involving human subjects under its purview prior to approval. (T-0: Paragraph 3.a.(2) of Enclosure 3)

(b) (Added)(AF) If there is more than one DoD IRB listed on the institution's DoD assurance, provide guidance regarding how to appropriately select the DoD IRB for each study.

(2) (Added)(AF) Establish a scientific review process for research conducted by the institution, and confirm there is a process for its consideration by the IRB. Ensure the scientific review is conducted for all non-exempt research involving human subjects conducted by the institution. (T-0: Paragraph 3.a.(2) of Enclosure)

(3) (Added)(AF) Ensure research in which the institution is engaged that requires higher level review (e.g., by the Secretary of Defense or ASD(R&E)) prior to start is forwarded to AFMSA/SGE-C for coordination. Ensures the submission package includes all final, IRB approved documentation and an analysis, supported by fact, of the compliance of the activity with applicable requirements.

c. Establish and maintain a DoD assurance and other appropriate Federal assurances, if the institution is engaged in non-exempt research involving human subjects (see Glossary).

(1) (Added)(AF) AF IOs shall obtain approval of their DoD assurance from AFMSA/SGE-C prior to engaging in non-exempt research involving human subjects. (T-0: Paragraph 3.a.(5) of Enclosure 3)

(2) (Added)(AF) Update the DoD assurance and submit to AFMSA/SGE-C when the IO or IRB Chair change. (T-0: Section 219.103 of Reference (c))

d. Evaluate and improve the institution's HRPP.

(1) (Added)(AF) Prior to initiation, the IO shall approve substantive changes to the institution's HRPP, and ensure AFMSA/SGE-C approval thereof. The IO should review the HRPP on an annual basis to ensure it remains current. (T-0: OASD(R&E) approved policy)

e. (Added)(AF) When appropriate, delegate the duties of this section, in writing, to a qualified member of the institution's executive staff, with authority to act on behalf of the institution, to serve as the AIO. Regardless of any formal delegation of an AIO, the IO, who is the most senior official, remains ultimately responsible for ensuring compliance of the institution's HRPP. (T-0: OASD(R&E) approved policy)

f. (Added)(AF) Provide an environment that strives to ensure compliance and ethical treatment of human subjects, while reducing the possibility for conflict of interest by personnel responsible for protecting human subjects. Disseminate information about HRPP compliance requirements, including that for prior review of activities that may include research involving human subjects, and identification of authorized EDOs, HRPOs, and/or IRBs. (T-0: OASD(R&E) approved policy)

g. (Added)(AF) Ensure staff receives training commensurate to their roles per section 5 of Enclosure 3. (T-0: Id)

h. (Added)(AF) Ensure prompt reporting to AFMSA/SGE-C any event requiring reporting to ASD(R&E) per DoDI 3216.02 or its References, including a summary of events, disposition, recommendations, and plans for corrective action and supporting documentation. AFMSA/SGE-C sends the reports to ASD(R&E), as required. (T-0: Id)

i. (Added)(AF) With respect to potential research misconduct in research involving human subjects, immediately notify AFMSA/SGE-C and provide an explanation of the circumstances if: public health or safety is at risk; the research institution's resources or interests are threatened or at risk; research activities are to be suspended because of the inquiry into or investigation of the allegation; there is a possible violation of civil or criminal law; action to protect the interests of those involved in the inquiry into or investigation of the allegation is required from the parent command; a premature public disclosure of the inquiry into or investigation of the allegation may compromise the process; or the research community or public should be informed. (T-0: Reference (bb), subparagraph E3.1.9.6.)

j. (Added)(AF) Establish policies and procedures to ensure compliant maintenance of research files and IRB records to include archival of records such as informed consent documents). (T-0: Section 15 of Enclosure 3)

k. (Added)(AF) Each IO of an AF institution supporting non-DoD conducted activities that are or may be research involving human subjects shall also: (T-0: OASD(R&E) approved policy)

(1) (Added)(AF) Either rely upon HRPO review provided by AFMSA/SGE-C or appoint, and obtain prior AFMSA/SGE-C approval of, the HRPO(s) upon which they will rely to ensure compliance of the institution's supported activities which may constitute research involving human subjects. If the IO will appoint a HRPO internal to the institution, establish procedures for HRPO review to be included in the institution's HRPP for AFMSA/SGE-C approval prior to implementation.

(2) (Added)(AF) Disseminate information about HRPO and other requirements applicable to non-DoD institution's activities when supported by AF, and establish internal processes to meet HRPO requirements, including coordination with the appropriate AF representative (e.g., the Contracting Officer) to ensure appropriate information is included in solicitations, awards, and agreements.

l. (Added)(AF) Establish procedures for ensuring investigators obtain prior written IO permission to target for participation in research subject populations under command of the IO (e.g., the IO's personnel and patients) and/or identifiable private information about such persons, prior to allowing access to such persons and/or information. In determining whether to permit the research, these supporting institutions should consider local mission requirements (e.g., would participation affect personnel ability to mobilize for readiness, to perform duties, or to be available for duty) (T-0: OASD(R&E) approved policy)

7. (Added)(AF) <u>AF IRB CHAIR.</u> Each IRB Chair shall: (T-0: OASD(R&E) approved policy)

a. (Added)(AF) Have at least one year of experience as a member of an IRB and demonstrated knowledge of HRPP requirements. AFMSA/SGE-C is the waiver approval authority for this requirement. Submit requests for waivers of this requirement with justification and description of the candidate's relevant experience.

b. (Added)(AF) Appoint a Vice Chair, when appropriate, to fulfill these duties in the absence of the IRB Chair.

c. (Added)(AF) Ensure the IRB considers scientific review and reviews research in accordance with Federal, DoD, and AF HRPP requirements. See subparagraph 3.a.(2) of Enclosure 3.

d. (Added)(AF) Review and sign IRB meeting minutes. Ensure minutes document IRB actions and determinations, e.g., as required per section 219.115 of Reference (c), and as necessary to memorialize resolution of compliance issues.

e. (Added)(AF) Consult with other committees, as appropriate (e.g., radiation committee, safety committee, privacy board).

f. (Added)(AF) Review and promptly report to the IO any item that requires reporting to AFMSA/SGE-C per paragraph 6.h. of this enclosure.

g. (Added)(AF) Appoint, at least annually, one or more individuals to randomly select and audit research records. This may include a review of subject eligibility, compliance with the IRB approved protocol, signed informed consent documents for proper execution, and observation of the consent process. The IRB Chair will review reports of these audits before discussion at an IRB meeting, and documentation in the IRB minutes.

h. (Added)(AF) Suspend research if necessary to ensure protection of human subjects pending IRB review, due to UPIRTSOs, adverse events associated with the use of drugs (see 21 CFR 312), adverse experiences associated with the use of biologics (see 21 CFR 600), unanticipated adverse device effects (see 21 CFR 812), significant deviations from approved studies, noncompliance, or other reasonable cause. (T-0: Id)

8. (Added)(AF) AF IRB SUPPORT PERSONNEL. IRB support personnel shall: (T-0: ASD(R&E) approved policy)

a. (Added)(AF) Coordinate IRB meetings and disseminate determinations in a timely manner.

b. (Added)(AF) Advise Principal Investigators (PIs) regarding protocol submission requirements.

c. (Added)(AF) Maintain records. Monitor completion of submissions and IRB records.

d. (Added)(AF) Generate and track correspondence

e. (Added)(AF) Manage daily operations of the IRB office.

f. (Added)(AF) Inform the IRB Chair and IO/AIO of events affecting the HRPP.

g. (Added)(AF) Prepare briefings and summaries of HRPP activities for the IO/AIO, as needed.

h. Submit to AFMSA/SGE-C, prior to start, all research described under subparagraph 3.b.(1) of Enclosure 3. Promptly submit to AFMSA/SGE-C for random and/or for cause audits all other non-exempt research involving human subjects; coordinate resolution of any compliance issues raised upon audit of this research. Promptly submit to AFMSA/SGE-C for compliance review all approved IRB minutes. See paragraph 5.j. of this enclosure.

9. AF HRPO. Each AF HRPO at the institutional level, under the authority of their IO and AFMSA/SGE-C, shall: (T-0: ASD(R&E) approved policy)

a. (Added)(AF) Receive written delegation of HRPO authority from AFMSA/SGE-C and their IO/AIO, per their institution's HRPP, prior to making HRPO determinations.

b. (Added)(AF) Be a DoD employee qualified through experience, expertise, and training to ascertain the acceptability of a non-DoD institution's proposed activity, while being sufficiently removed from the activity to avoid the appearance of a conflict of interest.

c. Complete initial and ongoing HRPO training, as required by AFMSA/SGE-C.

d. (Added)(AF) Conduct timely review of each non-DoD institution's activities that may include research involving human subjects (i.e., the protocol and all attachments) in accordance with their agreement with DoD (e.g., DFARS clause 252.235-7004, comparable grant, CRADA and other agreement) and this Instruction.

e. (Added)(AF) Communicate and provide guidance on HRPP requirements applicable to AF supported research involving human subjects conducted by non-DoD institutions.

f. (Added)(AF) Document and maintain records of each HRPO determination.

g. (Added)(AF) Coordinate with appropriate personnel (e.g., government Contracting Officer or DoD Program Manager) to obtain necessary documentation and information to enable approval and continuing oversight, as required.

h. (Added)(AF) Notify the IO of the supporting AF institution regarding research that requires higher level review (e.g., waiver of informed consent under section 980 of Reference (g)) prior to start.

i. (Added)(AF) Promptly submit to AFMSA/SGE-C a complete copy of all research reviewed, with the HRPO determination letter and support documentation, for review per paragraph 5.j. of this enclosure. Submit to AFMSA/SGE-C for final coordination any research involving human subjects that requires ASD(R&E) approval prior to start.

j. (Added)(AF) Ensure any DoD institutions engaged in activities related to those under HRPO review receive IRB or EDO review, as required, prior to start in accordance with section 3 of Enclosure 3. (T-0: Id)

10. (Added)(AF) <u>AF EDO.</u> Each AF EDO, under authority of their IO and AFMSA/SGE-C, shall: (T-0: ASD(R&E) approved policy,)

a. (Added)(AF) Receive written delegation of EDO authority from their IO/AIO and AFMSA/SGE-C prior to making any EDO determinations.

b. (Added)(AF) Be a DoD employee sufficiently qualified through appropriate training and experience to ascertain the acceptability of a proposed activity, while being sufficiently removed from the activity to avoid the appearance of a conflict of interest.

c. (Added)(AF) Complete initial and ongoing EDO training, as required by AFMSA/SGE-C.

d. (Added)(AF) Review activities to determine whether they are:

(1) Research involving human subjects per section 219.102 of Reference (c),

(2) Human subject research eligible for exemption from the requirement for IRB review per section 219.101(b) of Reference (c), or

(3) Research involving human subjects that requires IRB approval prior to start per part 219 of Reference (c).

e. (Added)(AF) Document and maintain records of each EDO determination, including a brief justification for the determination made and a citation to the exempt category, if applicable.

f. (Added)(AF) Advise the Principal Investigator (PI) of the determination and, if the activity requires IRB approval prior to start, refer to an IRB.

g. (Added)(AF) Ensure any non-DoD institutions engaged in activities both related to those under EDO review and covered by a non-DoD HRPP determination (e.g., from a non-DoD IRB) receive HRPO review prior to start per section 4 of Enclosure 3.

11. (Added)(AF) AF PI. Each PI of AF conducted research involving human subjects shall:

a. (Added)(AF) Manage and be responsible for supervision of all research conducted under the PI. (T-0: AF Issued DoD Assurance, Part 2, Paragraph 3.a.)

b. (Added)(AF) Promptly comply with IRB direction and local requirements. (T-0: Section 219.103 of Reference (c))

c . (Added)(AF) Prior to start of an activity that is or may be research involving human subjects, obtain written determination from an appropriate EDO or an IRB per paragraphs 6.a.(1)(a)1. and 10.d. of this enclosure, and the PI's IO/AIO per paragraph 6.a.(2) of this Enclosure. PIs are not authorized to make such determinations for their own activities. (T-0: Paragraphs 1.c.(7) and 3.a.(5) of Enclosure 3)

d. (Added)(AF) Notify the IRB, in accordance with applicable requirements and local policies, and in writing when possible, of UPIRTSOs and non-compliance. Propose protocol changes to minimize risks to subjects related thereto. (T-0: Section 219.103 of Reference (c))

e. (Added)(AF) Report conflicts of interest to the IO and IRB before engaging in human subject research and when conflicts arise during the conduct of research. (T-0: Paragraph 1.c.(7) of Enclosure 3)

f. (Added)(AF) Maintain research records (e.g., protocol, signed informed consent documents, IRB correspondence, and data) for at least three years after the research ends or for the length of time specified in applicable regulations, or institutional or sponsor requirements, whichever is longer. (T-0: Paragraph 15 of Enclosure 3,)

(1) (Added)(AF) Provide research records for maintenance, in accordance with local policy, to the assured institution under which the research is conducted upon completion of the research or reassignment, whichever comes sooner. (T-1)

ENCLOSURE 3

PROCEDURES

1. DoD COMPONENT HRPP MANAGEMENT PLAN

a. The DoD Component HRPP management plan shall include, by reference, DoD Component policies to implement the procedures set forth in this enclosure and identify the responsible DoD Component office(s) for actions identified in this Instruction. DoD Component policies may be more restrictive than the requirements in this Instruction, but they may not be less restrictive. They may also impose additional requirements needed to implement this Instruction.

b. The plan shall identify a single, senior official having the authority and responsibility for implementing the DoD Component HRPP management plan. This authority shall not be delegated lower than the general or flag officer (GO/FO), Senior Executive Service (SES), or equivalent level. All authorities delegated by the Head of the OSD or DoD Component must be identified in the management plan.

c. The plan shall reference DoD Component policies and procedures that:

(1) Direct each institution within the DoD Component conducting or supporting research involving human subjects to establish an HRPP that is compliant with this Instruction and the DoD Component's HRPP management plan.

(a) (Added)(AF) An AF institution whose activities related to research involving human subjects are limited to rarely (i.e., less than 5 instances per year) doing either or both of the following activities may, in lieu of adopting its own HRPP, rely upon the HRPP of other DoD institutions providing HRPO, IRB, or EDO services required by this instruction (e.g., AFMSA/SGE-C):

1. Supporting (but not engaging in) research involving human subjects, and/or

2. Engaging in exempt research involving human subjects per paragraph 219.101(b) of Reference (c).

(b) (Added)(AF) An AF institution is not considered to be supporting or conducting research involving human subjects when their personnel engage in non-exempt research involving human subjects while covered under the DoD assurance and HRPP of another DoD institution (e.g., via execution of an Individual Investigator Agreement). Under these circumstances, the AF institution would not be required to have an HRPP unless other facts triggered this requirement (e.g., support of more than 5 research protocols involving human subjects within a year).

(2) Describe DoD Component oversight of each institution's HRPP.

(a) (Added)(AF) AFMSA/SGE-C oversees each AF institution's HRPP by performing the tasks described in section 5 of Enclosure 2.

(3) Describe DoD Component administrative review of DoD-conducted and -supported research involving human subjects (see sections 3 and 4 of this enclosure for details).

(4) Delineate institutional responsibilities when performing research involving human subjects in collaboration with another DoD Component. These responsibilities shall include establishing written agreements for tasks such as minimizing the number of institutional review boards (IRBs) and DoD Components that review and approve the research (see sections 3 and 4 of this enclosure for details). DoD Component policies and procedures shall include a requirement to justify the duplication of reviews of protocols (for example, IRB and Component Headquarters reviews).

(a) (Added)(AF) AFMSA/SGE-C may satisfy the requirements for DoD Component review per section 3 of this enclosure, or HRPO review per section 4 of this enclosure, via deferral to another DoD Component's equivalent process, documented in writing.

(5) Outline education and training for implementation, management, and oversight of this Instruction (see paragraph 1.f. of Enclosure 2 and section 5 of this enclosure for details).

(6) Address the management of allegations and findings of noncompliance concerning DoD-conducted and -supported research involving human subjects (see section 16 of this enclosure for details).

(7) Identify and manage conflicts of interest, not limited to financial, for DoD personnel involved in the HRPP.

(8) Require a process to evaluate and improve the DoD Component's implementation of its HRPP management plan down to the level of the institutional HRPP.

d. A DoD Component may rely on another DoD Component for implementation of elements of the management plan except for designation of the single, senior official responsible for the management plan identified in paragraph 1.b. of this enclosure. Any such reliance must be reflected in the DoD Component's HRPP management plan.

2. REQUIREMENTS FOR A FEDERAL ASSURANCE

a. Activities for Which an Institution is Required to Have a Federal Assurance. Any institution engaged in non-exempt research involving human subjects that is conducted or supported by the Department of Defense shall have a Federal assurance consistent with section 219.103 of Reference (c) and acceptable to the funding agency.

(1) A DoD institution engaged in non-exempt research involving human subjects shall have a DoD assurance of compliance. Additionally, a DoD institution shall have an HHS assurance when engaged in non-exempt research involving human subjects funded by HHS (unless HHS will accept a DoD assurance). When conducting HHS-funded research involving human subjects, the DoD institution must follow this Instruction and any additional HHS requirements.

(a) (Added)(AF) The institution should be defined in the DoD assurance at the most senior level possible to ensure appropriate command-level oversight to allow IO/AIO awareness of the institution's HRPP and research activities. If an institution is defined to include groups outside the authority of the IO, the IO shall establish a memorandum of agreement with the outside entity. (T-0: OASD(R&E) approved policy)

(b) (Added)(AF) AF accepts DoD assurances issued by other DoD Components. IRBs reviewing research conducted by other DoD Components should ensure the scope of the other DoD Component's assurance covers the research. See subparagraph 5.d.(1), Enclosure 2.

(2) In complying with the requirements of section 219.103 of Reference (c), a non-DoD institution that is engaged in DoD-supported non-exempt research involving human subjects:

(a) Need not have a DoD assurance if it has an existing Federal assurance appropriate for the research being conducted. If the institution does not have a Federal assurance, the institution must provide either a DoD assurance to the DoD Component supporting the research or a Federal wide assurance to HHS, Office for Human Research Protections. Alternatively, if the institution does not have a Federal assurance, the researcher may use an Individual Investigator Agreement to associate with an institution having a Federal assurance and thus fulfill the requirement of conducting non-exempt research involving human subjects under an approved Federal assurance. In summary, all researchers conducting non-exempt research involving human subjects must be covered either directly under their institution's Federal assurance or indirectly using an Individual Investigator Agreement.

(b) Shall comply with the terms of its Federal assurance, applicable sections of this Instruction, and relevant policies of the supporting DoD Component.

(3) All institutions providing a DoD assurance to a designated DoD Component office shall include the items identified in section 219.103(b) of Reference (c).

(a) All institutions shall identify at least one IRB on their DoD assurance. DoD institutions shall identify all IRBs that are internal to the institution on their DoD assurance.

(b) When any institution relies upon another institution's IRB, there must be a written agreement defining the responsibilities and authorities of each organization in complying with the terms of each institution's Federal assurance and this Instruction (e.g., an Institutional Agreement for IRB Review). The existence of a DoD Institutional Agreement for IRB Review

or a similar agreement will satisfy the Federal assurance requirements at sections 219.103(b)(2)-(5) of Reference (c).

1. (Added)(AF) Submit to AFMSA/SGE-C all Institutional Agreements for IRB Review (IAIR) involving AF institutions (i.e., as either the institution relying on the IRB services or the institution supplying the IRB services). (T-0: OASD(R&E) approved policy)

2. (Added)(AF) Upon submission of the IAIR to AFMSA/SGE-C, an AF institution's DoD assurance will be deemed updated to include any new IRBs supplying IRB services to the AF institution. (T-0: OASD(R&E) approved policy)

b. Activities for Which an Institution is not Required to Have a Federal Assurance

(1) An institution is not required to have a Federal assurance if its personnel only conduct research that does not involve human subjects or the research involving human subjects meets at least one of the exemption criteria in section 219.101(b) of Reference (c).

(2) An institution that is only providing resources to support research involving human subjects (see Glossary definition of DoD-supported research involving human subjects) is not required to have a Federal assurance unless its involvement also meets the definition of being engaged in non-exempt research involving human subjects. When a DoD institution passes resources to another institution that will not be engaged in research, but will only transfer the resources to a third institution that will engage in research involving human subjects, the pass through institution is not required to have a Federal assurance. The institution engaged in non-exempt research involving human subjects must have a Federal assurance.

(3) An institution is not required to have a Federal assurance if it is collaborating in a research protocol that is non-exempt research involving human subjects and the institution's role in the collaborative research is limited to any of the following:

(a) Specific tasks that do not involve research involving human subjects; or

(b) Specific tasks that do not include the collection or handling of identifiable data or specimens. Research in which the human subjects' data or specimens are coded and the institution is prevented from having access to the code are considered non-identifiable for the purpose of this subparagraph.

(4) A DoD institution that does not meet the criteria for requiring a Federal assurance but conducts only exempt research involving human subjects or supports research involving human subjects must have an HRPP approved by its DoD Component that includes relevant policies and procedures to ensure compliance with this Instruction.

3. DoD-CONDUCTED RESEARCH INVOLVING HUMAN SUBJECTS

a. DoD Institutional Approval and Oversight

(1) DoD institutions conducting intramural research as defined in the Glossary involving human subjects shall have procedures to ensure appropriate regulatory determinations for activities that constitute research, activities that constitute research involving human subjects, or activities that are research involving human subjects but that meet the exemption criteria in section 219.101(b) of Reference (c). Such procedures shall include the designation, oversight, and appropriate training of DoD personnel.

(a) (Added)(AF) AF authorizes only AFMSA/SGE-C, IRBs, and EDOs to make official determinations regarding whether activities are not research involving human subjects, exempt research involving human subjects per section 219.101(b) of Reference (c), or research involving human subjects that requires IRB approval prior to initiation per Reference (c). (T-0: OASD(R&E) approved policy)

(b) (Added)(AF) AFMSA/SGE-C must approve each new EDO prior to start. (T-0: OASD(R&E) approved policy)

(2) The DoD institution shall have policies and procedures to require scientific review of non-exempt research involving human subjects and to ensure this review is considered during the IRB review process.

(3) IRBs may use expedited review procedures under section 219.110(a) of Reference (c) to review minimal risk, non-exempt research involving human subjects using materials (e.g., data, documents, records, or specimens) that have previously been collected for any purpose, provided the materials were not collected for the currently proposed research.

(4) When the research is being conducted in a foreign country whose laws and regulations are applicable to that research, the DoD institution shall confirm that all applicable national laws and requirements of the foreign country have been met in addition to the requirements in this Instruction. The IRB shall also consider the cultural sensitivities in the setting where the research will take place.

(a) (Added)(AF) When the above paragraph is applicable, these requirements must be met before the IRB approves research involving human per the requirements of sections 219.103, 219.107, and 219.111 of Reference (c). (T-0: Id)

(b) (Added)(AF) The IRB must document the source of information about the foreign research context in writing and maintain this with the research records (e.g., via letters from consultants and/or IRB minutes of meeting discussions in which consultants participated). Consultants participating in IRB meetings may not vote unless they are IRB members. (T-0: OASD(R&E) approved policy)

(5) The DoD institution shall have policies and procedures to ensure the research involving human subjects has been approved by all required organizations before human subjects are recruited or any other research activities with human subjects begin. The IRB may approve a research protocol contingent upon its approval by other organizations (e.g., required reviews can be conducted in parallel).

(6) An IRB, in accordance with part 219 of Reference (c), shall approve all non-exempt research involving human subjects before any activities that involve human subjects can begin. An official cannot approve research that has been disapproved by the IRB in accordance with part 219 of Reference (c) (i.e., an IRB disapproval of a protocol cannot be overturned). The IRB must provide oversight of the ongoing research and review such research at intervals appropriate to the degree of risk, but not less than once per year.

(7) DoD institutions shall rely on an IRB whose membership meets the requirements in subparagraphs 3.a.(7)(a) through (d). In special circumstances, DoD institutions may rely on a non-Federal IRB if the conditions in subparagraph 3.a.(8) of this section are met.

(a) DoD IRBs shall consist of members who are Federal employees; Service members; individuals covered by sections 3371-3376 of title 5, U.S.C. (also known as "The Intergovernmental Personnel Act of 1970, as amended") (Reference (m)); or individuals appointed as experts or consultants in accordance with section 3109 of Reference (m).

(b) For DoD IRBs, the requirement to have a non-affiliated IRB member (section 219.107(d) of Reference (c)) can be fulfilled by a person who meets the criteria in subparagraph 3.a.(7)(a) of this section and is from an organization that is not part of the institution as defined on the institution's Federal assurance. DoD IRBs shall designate at least one alternate for the non-affiliated member. Although the presence of a non-affiliated member is not a requirement to have a quorum, the designation of one or more alternates will increase the likelihood that a non-affiliated member is present at the meetings.

(c) The IRB shall also have a scientist and a non-scientist to meet the requirements in section 219.107(c) of Reference (c). A member whose primary concerns are in a non-scientific area (i.e., the non-scientist) must be present to have a quorum at convened meetings. The non-affiliated position and the non-scientist position may be filled by the same person, or the non-affiliated position and the scientist position may be filled by the same person.

(d) The DoD institution shall consider including one or more community members on the IRB who are familiar with the perspectives of the human subjects (i.e., the community being recruited) commonly recruited and vulnerable subjects recruited by the institution. Community members may or may not be affiliated with the institution or have a scientific background. The appointment of the community members must comply with subparagraph 3.a.(7)(a) of this section.

(e) DoD IRBs may consult with subject matter experts (e.g., in science, in statistics, in ethics, for the subject population) who are not Federal employees or board members, but these consultants may not vote.

(8) DoD institutions engaged in non-exempt research involving human subjects and collaborating with a non-DoD institution may rely on a collaborating non-DoD institution's IRB if these minimum conditions are met:

(a) The DoD Component determines the collaborating non-DoD institution has an appropriate Federal assurance.

1. (Added) (AF) OASD(R&E) has granted an exception of applicability of the above paragraph with respect to requiring a Federal assurance for a non-DoD institution whose IRB a DoD Component will rely for the limited purpose of allowing DoD assured institutions to rely upon the NCI's Central IRB (CIRB) for National Clinical Trails Network (NCTN) activities.

(b) The involvement of DoD personnel in the conduct of the research involving human subjects is secondary to that of the non-DoD institution.

(c) The DoD institution, the non-DoD institution, and the non-DoD institution's IRB have a written agreement defining the responsibilities and authorities of each organization in complying with the terms of the Federal assurances and this Instruction (i.e., have an Institutional Agreement for IRB Review or similar agreement). The DoD Component shall approve the terms of the agreement prior to the DoD institution's engagement in the research involving human subjects.

(d) The DoD Component must conduct an appropriate administrative review of the research involving human subjects to ensure it is in compliance with DoD policies and procedures prior to the DoD institution's engagement in the research.

b. DoD Component Review and Oversight

(1) At a minimum, the DoD Components must conduct an administrative review and approve all research involving non-exempt human subjects approved by a DoD institution when any of these conditions occur:

(a) The research will be conducted in a foreign country unless one of the following conditions apply:

1. The research will be conducted by an established DoD overseas research institution and the research will be conducted in the host country, or

2. The research will be conducted by a DoD overseas institution and will include only DoD personnel or U.S. citizens as human subjects.

(b) The research involves a collaboration with a non-DoD institution and the DoD institution is relying on the non-DoD institution's IRB, which is not composed of Federal

employees (i.e., the research is approved by the IRB using the criteria described in subparagraph 3.a.(8)) of this section.

(c) The research permits a waiver of informed consent under paragraph (b) of section 980 of Reference (g).

(d) The research involves any fetal research covered under sections 289g–289g-2 of Reference (j).

(e) The research is required to be approved by either the ASD(R&E) or the Head of the OSD or DoD Component as delegated by the ASD(R&E) (e.g., the requirements in sections 7, 9, or 13 of this enclosure apply).

(f) (Added)(AF) The research has been determined by an AF IRB to involve greater than minimal risk to subjects. (T-0: OASD(R&E) approved policy)

1. NCI's NCTN activity approved by an AF IRB are excepted from the requirement for AFMSA/SGE-C review and approval prior to start. Instead, they will be submitted to AFMSA/SGE-C for potential audit, per paragraph 5.j. of Enclosure 2.

(g) (Added)(AF) The research is a NCTN activity and the engaged DoD institution is relying upon the NCI's CIRB. See paragraph 3.a.(8)(a)1. of this Enclosure.

(h) (Added)(AF) The research involves biological or chemical warfare agents or weapons and is not prohibited by 50 U.S.C. 1520a. (T-0: OASD(R&E) approved policy)

(i) (Added)(AF) The activity is either exempt (per section 219.101(b) of Reference (c)) or non-exempt research involving human subjects and involves collecting statistical information under a promise of confidentiality per the Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA), consistent with section 512 of Public Law 107-347 (Reference (k) . Submit this research to AFMSA/SGE-C with documentation of approval of SAF/CIO A6. (T-0: OASD(R&E) approved policy)

(j) (Added)(AF) The research involves an FDA regulated investigational drug or investigational device. (T-0: OASD(R&E) approved policy,)

(k) (Added)(AF) A proposed substantive change to approved research makes it fall within a category requiring AFMSA/SGE-C approval prior to start per subparagraph 3.b.(1) of this enclosure. (T-0: OASD(R&E) approved policy)

(2) The DoD Component administrative review must be conducted before the research involving human subjects can begin to ensure compliance with all applicable regulations and policies, including any applicable laws and requirements and cultural sensitivities of a foreign country if conducted in a foreign country. This Component review is not intended to be an additional IRB review.

(3) (Added)(AF) AFMSA/SGE-C performs administrative reviews and provides approvals required per this section. (Enclosure 2, Paragraph 5.e.)

4. RESEARCH INVOLVING HUMAN SUBJECTS CONDUCTED BY A NON-DoD INSTITUTION

a. Clause in Contracts and Agreements. The DoD Component must ensure the institution conducting the research involving human subjects is aware of its obligation to comply with the requirements of this Instruction and part 219 of Reference (c).

(1) Contracts for DoD-supported research involving human subjects must contain the Defense Federal Acquisition Regulation Supplement (DFARS) clause in accordance with section 252.235-7004 of title 48, CFR (Reference (n)). In addition to identifying contractor requirements and responsibilities, this clause also describes the role of the DoD Human Research Protection Official (HRPO). Comparable agreements not subject to section 252.235-7004 of Reference (n) (e.g., grants, assistance agreements, and cooperative research and development agreements) must contain language affirming the responsibilities of the non-DoD institution as required by Parts 22 (Appendix B), 37 (Appendix D), and 219 of Reference (c).

(a) (Added)(AF) AF institutions providing support to non-DoD institutions for the performance of activities that may include research involving human subjects will provide the supported non-DoD institution with contact information for the HRPO (e.g., at the time of solicitation, the award, or soon after award). (T-0: OASD(R&E) approved policy)

(2) The DFARS clause (or similar language) is not required to be included in an agreement with another Federal department or agency that has adopted the Common Rule. Approval by the HRPO is not required. The Federal department or agency may apply its own HRPP requirements in lieu of this Instruction. However, the Federal department or agency must comply with the requirements in sections 7, 9, 13, and 17 of this enclosure and the requirements of Reference (f).

(a) (Added)(AF) When an AF institution executes an agreement with another Federal department or agency in order to support activities that could include research involving human subjects in which the Federal department or agency will not be engaged, it should include the DFARS clause or similar language. In light of the limited involvement provided by the Federal department or agency here, HRPO oversight should be viewed as an important tool to help ensure compliance. (T-0: OASD(R&E) approved policy)

b. Non-DoD Institutional Responsibilities

(1) The non-DoD institution shall comply with the terms of the DFARS clause or comparable language used in the agreement with the DoD Component supporting the research involving human subjects, as provided in subparagraph 4.a.(1) of this section.

(a) (Added)(AF) Successful completion of HRPO review is required prior to initiation of AF supported research involving human subjects. Submit all required paperwork for contracts, grants, and other awards to enable HRPO review (see paragraph 4.c. of this enclosure). The non-DoD institution shall ensure receipt of confirmation that the HRPO review is complete and that the activity is compliant prior to initiation of the research, e.g., prior to or after award but before exercising or funding a contract line item. (T-0: OASD(R&E) approved policy)

(b) (Added)(AF) Provide to the HRPO written documentation of IO/AIO approval of each engaged DoD institution and IO/AIO permission from each institution providing support to the research, e.g., via provision of facilities, equipment, or personnel used for the research. (T-0: Paragraphs 6.a.(2) of Enclosure 2, and 6.l.)

(2) When a non-DoD institution is conducting non-exempt research involving human subjects, the IRB review must consider the scientific merit of the research, as required by section 219.111 of Reference (c). The IRB may rely on outside experts to provide an evaluation of the scientific merit.

(3) IRBs may use expedited review procedures under section 219.110(a) of Reference (c) to review minimal risk, non-exempt research involving human subjects using materials (e.g., data, documents, records, or specimens) that have previously been collected for any purpose, provided the materials were not collected for the currently proposed research.

(4) To the extent provided in section 219.103 of Reference (c), the non DoD-institution shall promptly notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

(5) Non-DoD institutions shall comply with requirements of this Instruction applicable to them. They are not required to comply with provisions of this Instruction either solely directed to actions of the DoD Components or specifically limited to DoD-conducted research involving human subjects.

c. DoD Component Review, Approval, and Oversight

(1) When the contract or other agreement may include research involving human subjects and if the non-DoD institution determines either the activity is not research involving human subjects or is exempt research involving human subjects, the HRPO must concur with the performing institution's determination before activity can begin.

(a) (Added)(AF) For the purposes of compliance with the above paragraph, submit to the HRPO the non-DoD institution's determination letter and supporting

documentation considered by the institution in making the determination (e.g., the protocol describing the activity, data collection tools, advertisements, subject information sheets, etc.). The letter should provide a justification for the determination supported by facts and regulatory citations (e.g., applicable exempt category per section 219.101(b) of Reference (c)). (T-0: OASD(R&E) approved policy)

(b) (Added)(AF) The HRPO has authority to concur, require modifications in (to secure concurrence), or nonconcur with non-DoD institutions' determinations covered by the above paragraph. (T-0: OASD(R&E) approved policy)

(c) (Added)(AF) When unable to concur with the non-DoD institution's determination, HRPO will provide written documentation of its decision, which shall include the decision's rationale, relevant regulatory citations, and, if appropriate, modifications required to support a finding of compliance and thus, HRPO concurrence. (T-0: OASD(R&E) approved policy)

(2) If the non-DoD institution determines the activity is non-exempt research involving human subjects, the HRPO must perform an administrative review of the research before the activities that involve human subjects can begin (e.g., human subject recruitment and data collection). Such review and approval shall be based on confirmation that the research and non-DoD institution are in compliance with applicable requirements of this Instruction and Parts 22 (Appendix B), 37 (Appendix D), and 219 of Reference (c). At a minimum, the HRPO must:

(a) Confirm the non-DoD institution has a Federal assurance appropriate for the research in question (see paragraph 2.a. of this enclosure).

(b) Review the research protocol and accept the IRB determination of level of risk and approval of the study for compliance with this Instruction.

(c) Review and accept IRB-approved substantive changes to an approved research protocol before they are implemented.

(d) Ensure the IRB conducts an appropriate continuing review at least annually.

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

1. (Added)(AF) When the above paragraph is applicable, these requirements must be met before the IRB approves research involving humans per the requirements of sections 219.103, 219.107, and 219.111 of Reference (c). (T-0: OASD(R&E) approved policy)

2. (Added)(AF) The HRPO must receive documentation of IRB consideration of foreign requirements prior to their approval; for acceptable examples, see subparagraph 3.a.(4)(b) of this enclosure. (T-0: OASD(R&E) approved policy)

(f) (Added)(AF) The HRPO must receive documentation supporting an assessment of the institution's qualifications to conduct research involving human subjects per Enclosure 3, Section 5.d. (T-0: Id.)

(3) Upon receipt of notifications directed in subparagraph 4.b.(4) of this section, the supporting DoD Component shall promptly review the report and determine if further review of any or all the institution's research involving human subjects that is supported by the DoD Component is warranted. When appropriate, the DoD Component may defer its investigation to an ongoing Federal investigation. The DoD Component shall notify the ASD(R&E) in accordance with paragraph 3.f. of Enclosure 2 and section 16 of this enclosure.

(a) (Added)(AF) The HRPO shall perform the initial review required per the above paragraph and submit an analysis of the report, supported by facts and appropriate regulatory citations, to AFMSA/SGE-C. (T-0: OASD(R&E) approved policy) AFMSA/SGE-C will notify OASD(R&E) per paragraph 5.p. of Enclosure 2.

(4) DoD Components conducting a for-cause review of research conducted by a non-DoD institution shall evaluate and ensure the adequacy of human protection in DoD-supported programs and provide recommendations to the DoD Component about allowing continued DoD support of research involving human subjects, suspending the research until necessary changes have been made, or terminating the research.

(a) (Added)(AF) The HRPO shall report findings of any for-cause reviews of non-DoD institutions to the supporting AF institution and to AFMSA/SGE-C with appropriate recommendations to ensure continued protection of human subjects. (T-0: OASD(R&E) approved policy)

(5) (Added)(AF) The HRPO should communicate with the DoD institution supporting the research regarding all activities reviewed under this section. The supporting DoD institution should evaluate HRPO's determination and notify the supported non-DoD institution regarding any action required, consistent with applicable requirements (e.g., contracts, grants, or other agreements).

(6) (Added)(AF) In order to make a determination under this section, HRPO must receive sufficient documentation of facts which, when viewed in light of applicable requirements, support a finding that the activity is compliant. (T-0: OASD(R&E) approved policy)

(7) (Added)(AF) AFMSA/SGE-C administrative review and approval is required prior to start of any category of non-DoD conducted activities approved by an AF IRB identified in section 3.b.1. of Enclosure 3. (T-0: OASD(R&E) approved policy)

5. EDUCATION AND TRAINING. The DoD Components shall ensure that all DoD personnel involved in the conduct, review, or approval of research involving human subjects, including the non-affiliated and prisoner representative members on the DoD IRB, receive initial and continuing education and training in compliance with the standards set forth by ASD(R&E) (see paragraph 1.f. of Enclosure 2 for details).

a. Initial and continuing education and training shall be commensurate with the duties and responsibilities of the DoD personnel.

b. All training and education of DoD personnel shall be documented.

c. Professional certification in the field of human research protection is encouraged for all DoD personnel involved in review and oversight of research involving human subjects.

d. When assessing whether to support or collaborate with a non-DoD institution for research involving human subjects, the DoD Components should evaluate the non-DoD institution's education and training policies to ensure the personnel are qualified to perform the research. The rigor of the evaluation should be appropriate for the complexity and risk of the research.

e. (Added)(AF) AF policy is to accept from any engaged DoD institution any HRPP training certificate documenting compliance with standards set forth by ASD(R&E) per this section; duplicate local HRPP training shall not be required. (T-0: OASD(R&E) approved policy)

6. SELECTION OF HUMAN SUBJECTS AND EVALUATING RISK

a. Selection of Human Subjects. The selection of human subjects reflecting gender and minority participation in DoD-conducted or -supported clinical research involving human subjects shall comply with section 252 of Public Law 103-160 (Reference (o)). The Head of the OSD or DoD Component may exercise the waiver authority under this law. This waiver authority may be delegated, as described in the Component's HRPP management plan, but not to an individual at the level of the institutional HRPP.

(1) (Added)(AF) AF/SG delegates authority to AFMSA/SGE-C to approve waivers under the above paragraph. Submit waiver requests to AFMSA/SGE-C with justification in light of applicable requirements and facts. (T-0: OASD(R&E) approved policy)

(2) (Added)(AF) The following categories of research involving human subjects are exempt from the requirements of the above paragraph:

(a) (Added)(AF) Research involving human subjects that does not constitute a clinical investigation as defined herein.

(b) (Added)(AF) Clinical investigations of conditions specific to a single gender (e.g., prostate cancer research is specific to males) need not include the inapplicable gender.

(c) Added) (AF) Contact AFMSA/SGE-C with requests to add other appropriate categories of standard exemptions to this section.

(3) (Added)(AF) Submit all clinical investigations seeking exemption under subparagraph 6.a.(2) above to the appropriate AF HRPP representative (AFMSA/SGE-C for AF-conducted clinical investigations; the HRPO for non-DoD conducted clinical investigations) with a justification, supported by relevant facts and regulatory analysis, with citations. (T-0: Enclosure 3, Paragraph 6.a.)

(4) (Added)(AF) Clinical investigations supported by AF and conducted by non-DoD institutions at non-DoD institutions shall make every effort to enroll women and minorities, as appropriate, but are not required to specifically target for recruitment military members per the above paragraph. (T-0: Enclosure 3, Paragraph 6.a.)

b. Evaluating Risk. The phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" in the definition of minimal risk (section 219.102(i) of Reference (c)) shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

7. ADDITIONAL PROTECTIONS FOR HUMAN SUBJECTS. In addition to the requirements of part 219 of Reference (c), additional safeguards described in this section shall be provided for human subjects in all DoD-conducted research involving human subjects who may be considered vulnerable due to their association with groups or populations specifically defined by Federal regulations in subparts B-D of Reference (h) and this Instruction. Similarly, as provided in Reference (n) or Parts 22 (Appendix B) and 37 (Appendix D) of Reference (c), such additional safeguards shall also be provided in comparable DoD-supported research involving human subjects. For purposes of this Instruction, actions authorizing or requiring any action by an official of HHS about any requirements of subparts B-D of Reference (h) shall be under the authority of the ASD(R&E). Investigators, IRBs, IOs, and DoD Component personnel reviewing research protocols shall consider the need for appropriate similar safeguards for other vulnerable populations, such as: research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of human subjects in circumstances that may warrant provision of additional protections. As appropriate, qualified individuals (e.g., research monitors, ombudsmen, advocates) may be appointed to perform oversight functions or assist the human subjects.

a. Pregnant Women, Fetuses, and Neonates as Subjects

(1) Non-exempt research involving pregnant women, fetuses, or neonates as human subjects must meet the additional relevant protections of subpart B of Reference (h), unless modified by this Instruction. Research involving pregnant women as subjects may be exempt from the requirements of part 219 of Reference (c) and subpart B of Reference (h) if the research meets the exemption criteria at section 219.101(b) of Reference (c). If the pregnant woman is a prisoner, then paragraph 7.b. of this section also applies. If the pregnant woman is a minor, paragraph 7.d. of this section also applies. For purposes of applying paragraph 7.a., the phrase "biomedical knowledge" in subpart B of Reference (h) shall be replaced with "generalizable knowledge" throughout the subpart.

(2) The applicability of subpart B of Reference (h) is limited to research involving:

(a) Pregnant women as human subjects involved in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus; or

(b) Fetus or neonate (see Glossary) as human subjects.

(3) Research involving human subjects using fetal tissue shall comply with sections 289g–289g-2 of Reference (j).

b. Prisoners as Subjects

(1) Research Intending to Include Prisoners as Subjects

(a) Research involving human subjects that includes prisoners must meet the additional relevant protections of subpart C of Reference (h), unless modified by this Instruction. If the prisoner is a pregnant woman, then paragraph 7.a. of this section also applies. If the prisoner is a minor, then paragraph 7.d. of this section also applies.

(b) Research intending to include prisoners as subjects cannot be reviewed by the IRB through an expedited review procedure.

(c) The IRB reviewing research intending to include prisoners as subjects shall be composed of at least one prisoner representative (see Glossary). The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison. The prisoner representative shall have knowledge of the culture(s) of the prisoners and knowledge of the prison operations. At least one prisoner representative must be present for a quorum.

(d) Research involving prisoners at prisons or other types of institutions may be subject to additional review by institution authorities (e.g., Bureau of Prisons).

(2) Categories of Allowable Research Involving a Prisoner. In addition to the four categories of permissible research involving human subjects identified in subpart C of Reference (h), two additional categories are allowable.

(a) Epidemiological research that meets the following criteria can also be approved in accordance with the requirements of subpart C of Reference (h) and the requirements of this Instruction:

1. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor associations for a disease.

2. The research presents no more than minimal risk.

3. The research presents no more than an inconvenience to the human subject.

4. Prisoners are not a particular focus of the research.

(b) Research involving human subjects that would meet the criteria described at section 219.101(b) of Reference (c) can be conducted, but must be approved by a convened IRB and meet the requirements of subpart C of Reference (h), this Instruction, and other applicable requirements.

(3) When a Subject Becomes a Prisoner

(a) When a previously enrolled human subject becomes a prisoner and the relevant research protocol was not reviewed and approved by the IRB in accordance with the requirements of subparagraphs 7.b.(1) and (2) of this section, the principal investigator shall promptly notify the IRB.

(b) If the principal investigator asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-subject may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the IO and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol.

(c) The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

(d) This type of request for change in the research protocol cannot be reviewed and approved by the IRB using expedited review procedures. The research involving human subjects does not have to meet one of the six allowable categories of research as described in subparagraph 7.b.(2) of this enclosure.

(e) If the research involving human subjects is conducted by a non-DoD institution, the non-DoD institution shall promptly report all decisions in this matter to the HRPO. If the research is conducted by a DoD institution, the IRB shall promptly report all decisions in this matter to the IO and to the DoD Component office conducting the reviews identified in paragraph 3.b. of this enclosure. For all DoD-conducted or -supported research involving human subjects, the applicable DoD Component office conducting the reviews identified in paragraphs 3.b. or 4.c. of this enclosure must concur with the IRB before the human subject can continue to participate while a prisoner. This approved change to a research protocol does not require ASD(R&E) approval.

c. Treatment of Detainees

(1) Research involving a detainee, as defined in DoD Directive 2310.01E (Reference (p)), as a human subject is prohibited.

(2) The prohibition in paragraph c.(1) of this section does not apply to activities covered by investigational new drug or investigational device provisions of Reference (d) when for the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to Reference (d) as investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices. Such permitted treatment involving detainees as subjects shall comply with all sections of this Instruction, including paragraphs 6.a., b., and d. of this section, as applicable.

d. Children as Subjects

(1) Research involving human subjects conducted or supported by the Department of Defense that recruits children to be subjects must meet the additional relevant protections of subpart D of Reference (h), unless modified by this Instruction. If the minor is a pregnant woman, then paragraph 7.a. of this section also applies. If the minor is a prisoner, paragraph 7.b. of this section also applies.

(2) The footnote in section 219.101(i) of Reference (c), prohibiting specific exemptions described in section 219.101(b) from applying to children, is also applicable to DoD-conducted or -supported research involving human subjects unless otherwise clarified in this Instruction.

e. DoD Personnel as Subjects

(1) Military Personnel as Subjects

(a) Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty. Additionally a Service member's ability to perform his or her military duties may be affected by participating during off-duty time (i.e., on leave or during non-duty hours). Therefore, Service members shall follow their Component and command's policies for approving off-duty employment or activities. The IRBs of DoD institutions or HRPOs may require Principal Investigators to confirm that a Service member's commander supports the member's participation in DoD-supported research involving human subjects.

(b) Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research involving human subjects covered by this Instruction.

(c) Superiors of Service members (e.g., unit officers, senior NCOs, and equivalent civilians) in the chain of command shall not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as human subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session.

(d) For research involving Service members as human subjects that has been determined to be greater than minimal risk and when recruitment occurs in a group setting, the IRB shall appoint an ombudsman. The ombudsman shall not be associated in any way to the research and shall be present during the recruitment in order to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor (see section 8 of this enclosure). For research involving Service members as human subjects, that has been determined to be NO greater than minimal risk and when recruitment occurs in a group setting, the IRB shall determine when it is appropriate to appoint an ombudsman for the purposes described in this paragraph. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

(2) DoD Civilians as Subjects

(a) DoD Civilians shall follow their organization's policies regarding the requirement to obtain permission to participate in research involving human subjects.

(b) Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research involving human subjects covered by this Instruction.

(c) Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) shall not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session.

(d) For research involving civilians as human subjects and when recruitment occurs in a group setting, the IRB shall discuss appointing an ombudsman for the purposes described in subparagraph e.(1)(d) of this section. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

8. RESEARCH MONITOR

a. For DoD-conducted research involving human subjects determined by the IRB to involve more than minimal risk to human subjects (as defined in section 219.102(i) of Reference (c)), and, to the extent provided pursuant to Parts 22 (Appendix B), 37 (Appendix D), and 219 of Reference (c) and Reference (n), comparable DoD-supported research, the IRB shall approve an independent research monitor by name. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or IO for research involving human subjects determined to involve minimal risk. There may be more than one research monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.

(1) The duties of the research monitor shall be determined on the basis of specific risks or concerns about the research. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis) and report their observations and findings to the IRB or a designated official.

(2) The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

(3) The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

(4) The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

b. The Heads of the OSD and DoD Components may waive the requirement to have a research monitor on a case-by-case basis when the inclusion of a research monitor is not necessary to provide additional protections for human subjects. This waiver authority may be delegated to a DoD official, as described in the Component's HRPP management plan, but not at or below the position of the institution's DoD IO.

(1) (Added)(AF) AF/SG delegates waiver approval authority under the above paragraph to AFMSA/SGE-C. Submit waiver requests with a justification in light of the facts and applicable requirements. (T-0: OASD(R&E) approved policy)

9. UNIQUE DoD LIMITATIONS ON WAIVER OF INFORMED CONSENT

a. Sections 219.116(c) and (d) of Reference (c) identify conditions where an IRB may waive informed consent for DoD-conducted and DoD-supported research involving human subjects. Section 980 of Reference (g) imposes limitations on waiving informed consent when using DoD appropriated funds. Section 980 of Reference (g) is applicable ONLY to DoD funded research involving a human being as an experimental subject as defined in the Glossary. The definition of research involving a human subject as an experimental subject is not the same as the definition of research involving human subjects. Section 980 of Reference (g) is not applicable to exempt research involving human subjects.

b. When the research meets the Glossary definition of research involving a human being as an experimental subject, informed consent must be obtained in advance from the experimental subject or the subject's legal representative consistent with part 219 of Reference (c) if the subject cannot consent. If consent is to be obtained from the experimental subject's legal representative, the research must intend to benefit the individual subject. The determination that research is intended to be beneficial to the individual experimental subject must be made by an IRB consistent with part 219 of Reference (c).

c. The requirement of paragraph 9.b. of this section may be waived by the ASD(R&E) if all the following conditions are met:

(1) The research is necessary to advance the development of a medical product for the Military Services.

(2) The research may directly benefit the individual experimental subject.

(3) The research is conducted in compliance with all other applicable laws and regulations.

d. The ASD(R&E) may delegate the waiver authority described in paragraph 9.c. to the Heads of the OSD and DoD Components if they have appropriate policies and procedures in their management plans. This authority is further delegable only to a DoD Component official who is a Presidential Appointee with Senate Confirmation.

10. PROTECTING HUMAN SUBJECTS FROM MEDICAL EXPENSES IF INJURED

a. DoD-Supported Research Involving Human Subjects. All non-exempt research involving human subjects shall, at a minimum, meet the requirement of section 219.116(a)(6) of Reference (c). The Common Rule does not require payment or reimbursement of medical expenses, provision of medical care, or compensation for research-related injuries.

b. DoD-Conducted Research Involving Human Subjects. The DoD Components shall establish procedures to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in DoD-conducted non-exempt research involving human subjects that involves more than minimal risk. Such procedures may consist of utilizing the Secretarial Designee program as described by section 108.4(i) of Reference (c) during the period of the human subject's involvement in the research, which may be extended further upon the approval of the USD(P&R). DoD Components may supplement this Secretarial Designee procedure with additional procedures consistent with applicable authority. This requirement does not apply when the Department of Defense is supporting the research but is not engaged in the non-exempt research involving human subjects (i.e., when the non-exempt research involving human subjects is performed solely by non-DoD institutions).

c. DoD Collaborative Research Involving Human Subjects

(1) When collaborating with a non-DoD institution, the DoD Components shall establish procedures comparable to those required by paragraph 10.b. of this section to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in non-exempt research involving human subjects and that are a direct result of research activities performed by DoD personnel. This does not apply to expenses resulting from the injury due to actions performed by the non-DoD institution(s).

(2) When DoD personnel are conducting the research involving human subjects at the collaborating institution and the Department of Defense does not have the primary involvement, the DoD Components are not required to have procedures to protect human subjects from medical expenses. For this purpose the determination of primary involvement shall be based on consideration of the type and portion of the DoD involvement in the collaborative research (e.g., research staff, human subjects, facilities, equipment, IRB, and all other assets).

(3) When the collaboration is such that it is difficult to separate DoD involvement from that of the non-DoD institution, the Head of the OSD or DoD Component may waive this requirement to have procedures to protect human subjects from medical expenses. This waiver authority may be delegated, as described in the Component's HRPP management plan, but not at or below the position of the institution's DoD IO.

11. COMPENSATION TO HUMAN SUBJECTS FOR PARTICIPATION IN RESEARCH

a. DoD-Conducted Research Involving Human Subjects

(1) When the Human Subjects Are On-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in DoD-conducted research while on duty (i.e., not on leave and participating during their duty hours) may be compensated up to $50 for each blood draw if the research meets the purpose of section 30 of title 24, U.S.C. (Reference (q)). Payment for blood draws may come directly from a Federal or non-Federal source. By permitting compensation for blood draws, Reference (q) provides an exception to section 5536 of Reference (m), which prohibits Federal personnel from being paid by any source other than their regular Federal salaries while they are on duty.

(b) Federal personnel participating as human subjects in DoD-conducted research while on duty may only be compensated for blood draws as described in this paragraph and may not be otherwise compensated for general research participation.

(2) When the Human Subjects Are Off-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in DoD-conducted research while off duty may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). Payment for blood draws may come from a Federal or non-Federal source.

(b) Additionally Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

(3) When the Human Subjects Are Not Federal Personnel

(a) Non-Federal personnel participating as human subjects in DoD-conducted research may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). Payment for blood draws may come directly from a Federal or non-Federal source.

(b) Additionally non-Federal personnel may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research. Payment for general research participation may come directly from a Federal or non-Federal source.

(4) (Added)(AF) AF will not accept voluntary services without compensation when such services may provide a basis for a future claim against the government. An individual may enter into an independent contractor relationship with the AF and participate for compensation, as authorized by applicable directives (e.g., Reference (ff)). Include one of the following statements in each informed consent document for AF conducted research involving human subjects. (T-0: Id.)

(a) (Added)(AF) If compensation is not provided, state there are no plans to provide compensation for participation in the research.

(b) (Added)(AF) If compensation is provided, state there are no plans to provide other compensation beyond that described in the informed consent document.

b. Non DoD-Conducted Research Involving Human Subjects

(1) When the Human Subjects Are On-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in research conducted by a non-DoD institution (whether or not the research is Federally funded) may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). By permitting compensation for blood draws, Reference (q) provides an exception to section 5536 of Reference (m), which prohibits Federal personnel from being paid by any source other than their regular Federal salaries while they are on duty.

(b) Federal personnel participating as human subjects in non-DoD-conducted research while on duty may only be compensated for blood draws as described in this paragraph and may not be otherwise compensated for general research participation, even if the research is not Federally funded or conducted.

(2) When the Human Subjects Are Off-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in Federally-funded human subject research conducted by a non-DoD institution may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). However, if the research is not Federally funded, the human subjects may be compensated for blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the blood draw unless it is prohibited by this Instruction or another policy (i.e., the $50 limitation per blood draw does not apply).

(b) Additionally Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for general research participation must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

(3) When the Human Subjects Are Not Federal Personnel

(a) Non-Federal personnel participating as human subjects in DoD-funded research may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q).

(b) Additionally non-Federal personnel may be compensated for participation in DoD-supported research for other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research. Payment for general research participation may come directly from a Federal or non-Federal source.

12. SERVICE MEMBERS AND THEIR STATUS AS ADULTS. For purposes of legal capacity to participate in DoD-conducted or -supported research involving human subjects, all active duty Service members and all Reserve Component members in a Federal duty status are considered for purposes of this Instruction to be adults. The participation of such members is not subject to requirements of paragraph 7.d. of this enclosure or subpart D of Reference (h) regarding research involving children or minors. When Service members are under 18 years of age, students at Service Academies, or trainees, the IRB shall carefully consider the recruitment process and the necessity to include such members as human subjects.

13. CLASSIFIED RESEARCH INVOLVING HUMAN SUBJECTS. For all DoD-conducted non-exempt research involving human subjects that involves classified information as defined in Executive Order 13526 (Reference (r)), and, to the extent provided pursuant to Parts 22, 37, and 219 of Reference (c) and Reference (n), comparable DoD-supported research, the additional requirements in this section apply. The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. If this activity is part of a classified program, this section does not apply if the information required to be contained in the research protocol or needed by either the IRB or the human subjects is not classified.

a. Secretary of Defense approval is required for all classified non-exempt research involving human subjects. Submission for approval shall be from the Head of the OSD or DoD Component conducting or supporting the non-exempt research involving human subjects. The request shall be coordinated with the ASD(R&E) and General Counsel of the Department of Defense after the IRB has approved the research.

b. Waivers of informed consent are prohibited.

c. Informed consent procedures shall include:

(1) Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.

(2) A statement that the research involving human subjects is classified and an explanation of the impact of the classification.

d. IRB approval process shall meet the following requirements:

(1) IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.

(2) At least one non-affiliated member shall be a non-Federal employee (other than as an individual appointed as an expert or consultant in accordance with section 3109 of Reference (m) for purposes of service on the IRB).

(3) Any IRB member who disagrees with a majority decision approving a project may appeal the decision to the Secretary of Defense. The appeal shall be included in the DoD Component's submission to the Secretary of Defense.

(4) The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

e. Disclosure or use of classified information must comply with the requirements of Reference (r) for access to and protection of classified information.

14. ADDITIONAL PROTECTIONS FOR CONFIDENTIALITY. This section outlines certain authorities that the DoD Components may consider using, subject to applicable requirements, for particular sensitive research activities when additional protections for confidentiality would improve participation and results.

a. Confidential Information Protection and Statistical Efficiency Act (CIPSEA) for Non-Statistical Agencies. Any DoD Component may use the authority pursuant to sections 501-513 of Reference (k) to assure that data or information acquired by the DoD Component under a pledge of confidentiality for exclusively statistical purposes shall be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent. Use of this authority is subject to the requirements of sections 512 and 523-525 of Reference (k) and of Reference (l), including that the research involving human subjects is conducted by a DoD Component or other Federal agency and not by a contractor, grantee, or other non-Federal entity, and that use of the authority is reported annually to OMB by the DoD Component.

b. CIPSEA for Statistical Agencies. Any DoD Component or unit thereof designated a statistical agency by the OMB pursuant to section 522 of Reference (k) and Reference (l) may designate agents (e.g., contractor, grantee, or other non-Federal entity under a qualifying agreement) that may assure that data or information acquired for the Component under a pledge

of confidentiality for exclusively statistical purposes shall be used exclusively for statistical purposes, and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent. Use of this authority is subject to the requirements of sections 512 and 523-525 of Reference (k) and of Reference (l).

c. Certificate of Confidentiality. A DoD Component or a contractor, grantee, or other non-Federal entity conducting DoD-supported research involving human subjects may request from the National Institutes of Health (NIH) of the Department of HHS a Certificate of Confidentiality pursuant to section 241(d) of Reference (j). Such a Certificate of Confidentiality authorizes persons engaged in biomedical, behavioral, clinical, or other research related to mission areas of the NIH to protect the privacy of human subjects of sensitive research against compulsory disclosure in any Federal, State, or local judicial, administrative, or legislative proceeding to identify human subjects. Issuance of any Certificate of Confidentiality is at NIH's discretion and is subject to the requirement of section 241(d) of Reference (j) and any other NIH guidelines.

d. (Added)(AF) All proposals to use authority under CIPSEA or a Certificate of Confidentiality must be coordinated with AFMSA/SGE-C prior to implementation. (T-0: OASD(R&E) approved policy)

15. RECORD KEEPING

a. Part 219 of Reference (c) requires all institutions engaged in DoD-conducted or -supported research involving human subjects to retain records for at least 3 years after the completion of the research. Research involving human subjects may be covered by other Federal regulations that impose longer record keeping requirements. The DoD Components may rely on the non-DoD institutions to keep the required records that were generated by the institution, or the DoD Components may make arrangements to transfer the records.

b. The DoD Components shall also retain records regarding the oversight of DoD Component-supported research involving human subjects for at least 3 years after the completion of the research, HRPP education or training program, or other action relevant to the HRPP. Additionally, the DoD Components shall keep all records regarding DoD Component waivers, exemptions, and extensions, and all DoD Component requests for exceptions, waivers, exemptions, and extensions submitted to the ASD(R&E) for action for at least 3 years after the completion of the research.

c. The DoD Components may be required to retain records for longer than specified in paragraphs 15.a. and 15.b. of this section. For example, some Health Insurance Portability and Accountability Act documentation is required to be retained for 6 years (in accordance with DoD 6025.18-R (Reference (s))). For complete recordkeeping guidance and instruction, the DoD Components shall consult their respective records disposition schedules.

d. Records maintained by non-DoD institutions that document compliance or noncompliance with this Instruction shall be made accessible for inspection and copying by authorized

representatives of the Department of Defense at reasonable times and in a reasonable manner as determined by the supporting DoD Component.

16. NONCOMPLIANCE WITH THIS INSTRUCTION. The DoD Components shall respond to allegations of noncompliance with this Instruction. For allegations that involve more than one DoD Component or a non-DoD institution, the involved institutions should jointly determine and assign executive responsibility for responding to the allegation(s). For allegations involving a non-DoD institution, the DoD Component supporting the research involving human subjects shall ensure the allegation is properly investigated and reported to the DoD Component. All findings of serious or continuing noncompliance with this Instruction that have been substantiated by inquiry or investigation shall be reported to the ASD(R&E) in a timely manner.

a. (Added)(AF) Submit such noncompliance to AFMSA/SGE-C, which shall report to ASD(R&E). (OASD(R&E) approved policy, T-0)

b. (Added)(AF) Each allegation of research misconduct in activities in which an institution is engaged must be processed in accordance with their HRPP procedures established under Reference (bb) and subparagraph 6.a.(5) of Enclosure 2. (T-0: Id.)

17. APPLICABILITY TO OTHER REQUIREMENTS. Compliance with this Instruction does not imply that all other applicable requirements have been met for DoD-conducted and -supported research involving human subjects. No DoD agency within the Intelligence Community shall sponsor, contract for, or conduct non-exempt research involving human subjects except in accordance with paragraph 2.10 of Executive Order 12333 (Reference (t)). Additionally, research involving human subjects using surveys, materials under the purview of the FDA, or individually identifiable health information may be subject to additional Federal or DoD requirements, such as those identified in Reference (s), DoD 5400.11-R (Reference (u)), and DoDI 6000.08 (Reference (v)). States may have differing definitions and protections for vulnerable populations. Research involving human subjects conducted in foreign countries may be subject to additional national and local requirements.

a. (Added)(AF) AFMSA/SG5I implements Reference (v) for the funding and administration of Clinical Investigation Programs.

18. CCHRPP MEMBERSHIP. The CCHRPP shall be composed of senior officials at the GO/FO, SES, or equivalent level. The Heads of the OSD and DoD Components with a DoD Component HRPP management plan shall each identify one member to represent their Component to the ASD(R&E). The Chair shall be designated by the ASD(R&E). The CCHRPP shall be supported by an Executive Secretariat (O-6 or equivalent level) composed of representatives from the DoD Components' human research protection oversight offices.

19. (Added)(AF) AF EMERGENCY USE OF A DRUG, DEVICE, OR BIOLOGICAL PRODUCT.

a. (Added)(AF) Emergency use of an investigational drug, device, or biological product under life-threatening circumstance for treatment purposes is not research.

b. (Added)(AF) The treating physician initiating emergency use procedures is responsible for compliance with applicable FDA regulations at Reference (d), to include reporting the emergency use to the IRB within five days after the use.

c. (Added)(AF) In a timely manner after completion of their review of the emergency use, the AF IRB shall forward documentation demonstrating regulatory compliance of the emergency use per Reference (d) to AFMSA/SGE-C, with patient identifiers redacted. AFMSA/SGE-C will review the use and concur, nonconcur, or concur with comments. (T-0: OASD(R&E) approved policy)

GLOSSARY

PART I. ABBREVIATIONS AND ACRONYMS

(Added)(AF) AF	**Air Force**
(Added)(AF) AF/SG	**Air Force Surgeon General**
(Added)(AF) AFMSA/SGE-C	**Research Oversight and Compliance Division**
(Added)(AF) AFMSA/SG5I	**Air Force Medical Support Agency Research and Innovations**
(Added)(AF) AIO	**Authorized Institutional Official**
ASD(HA)	Assistant Secretary of Defense for Health Affairs
ASD(R&E)	Assistant Secretary of Defense for Research and Engineering
CCHRPP	Coordinating Committee for Human Research Protection Programs
CFR	Code of Federal Regulations
CIPSEA	Confidential Information Protection and Statistical Efficiency Act of 2002
(Added)(AF) CIRB	**Central Institutional Review Board**
DFARS	Defense Federal Acquisition Regulation Supplement
(Added)(AF) DoD	**Department of Defense**
DoDD	Department of Defense Directive
(Added)(AF) EDO	**Exempt Determination Official**
FDA	Food and Drug Administration
GO/FO	general or flag officer
HHS	Health and Human Services
HRPO	human research protection official
HRPP	Human Research Protection Program
(Added)(AF) IAIR	**Institutional Agreement for IRB Review**
(Added)(AF) IIA	**Individual Investigator Agreement**
IO	institutional official
IRB	institutional review board
(Added)(AF) NCI	**National Cancer Center**
NCOs	noncommissioned officers
(Added)(AF) NCTN	**National Clinical Trails Network**
NIH	National Institutes of Health
(Added)(AF) OASD(R&E)	**Office of ASD(R&E)**
OMB	Office of Management and Budget
(Added)(AF) OSD	**Office of the Secretary of Defense**
OT&E	operational test and evaluation
(Added)(AF) OHRP	**Office for Human Research Protections**
P	**Principal Investigator**
RDT&E	research, development, test and evaluation
SES	Senior Executive Service
(Added)(AF) SGHARP	**AF/SG's Human and Animal Research Panel**
UPIRTSO	unanticipated problems involving risks to subjects or others

U.S.C.	United States Code
USD(P&R)	Under Secretary of Defense for Personnel and Readiness

PART II. DEFINITIONS

Unless otherwise noted, these terms and their definitions are for the purpose of this Instruction.

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

(Added)(AF) AIO. A person delegated authority and responsibility to fulfill the duties of the IO for the purposes of overseeing the institution's HRPP.

(Added)(AF) assurance. See Federal assurance.

classified research involving human subjects. Research involving human subjects where the protocol or other information required by the IRB for review and oversight or required or provided by the research subjects includes classified information, as defined in Reference (q).

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

(Added)(AF) clinical research involving human subjects. For the purposes of paragraph 6.a. of Enclosure 3, the term "clinical research involving human subjects" is synonymous with the term "clinical investigations", defined above.

continuing noncompliance. A pattern of noncompliance (see definition of noncompliance) that suggests the likelihood that, without intervention, instances of noncompliance will recur. A repeated unwillingness to comply with this Instruction or a persistent lack of knowledge of how to comply with this Instruction.

Common Rule. The regulation adopted by multiple Federal departments and agencies for the protection of human subjects in research. The Department of Defense's implementation of the Common Rule is part 219 of Reference (c); the Department of HHS's implementation of the Common Rule is subpart A of Reference (h).

detainee. Defined in Reference (p). (**Added)(AF) "Any person captured, detained, held, or otherwise under the control of DoD personnel (military, civilian, or contractor employee). It does not include persons being held primarily for law enforcement purposes, except where the United States is the occupying power." A detainee may also include the following categories: Enemy Combatant, Lawful Enemy Combatant, Unlawful Enemy Combatant, Enemy Prisoner of War, Retained Person, and Civilian Internee. These categories are defined in Reference (p).**

DoD-conducted research involving human subjects. Research involving human subjects that is performed by DoD personnel. Intramural research is one type of DoD-conducted research involving human subjects. See "engaged in research involving human subjects."

DoD personnel. DoD civilian employees and members of the military services.

DoD civilian employee. An individual meeting the definition of "employee" consistent with section 2105 of Reference (m). It includes employees of DoD Non-Appropriated Fund Instrumentalities; DoD civilian employees filling full-time, part-time, intermittent, or on-call positions; and individuals serving under personal services contracts consistent with section 2.101 of Reference (n). It excludes employees of contractors (other than personal services contractors) and foreign nationals of host countries.

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

DoD-supported research involving human subjects. Research involving human subjects for which the Department of Defense is providing at least some of the resources (see "research involving human subjects"). Resources may include but are not limited to funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by a non-DoD institution.

(1) (Added)(AF) An activity is not considered to be DoD-supported when a DoD employee either has been formally authorized to pursue an outside activity separate from their DoD position, or is in an off-duty status or otherwise not working in a DoD capacity, and if the activity does not otherwise involve the DoD.

(2) (Added)(AF) Legal transfer (e.g., through sale or donation) of equipment from the DoD to non-DoD institution, when not done by the DoD for the purpose of enabling specific research involving human subjects, severs the relationship with the DoD, and the transfer is not considered DoD support.

(Added)(AF) EDO. Serves as a local AF HRPP official delegated authority by the IO/AIO and AFMSA/SGE-C to ensure compliance of the AF institution's proposed activities with human subjects prior to initiation per section 10 of Enclosure 2.

(Added)(AF) emergency use. Use of an investigational drug, device, or biological product with a patient in a life-threatening situation in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval. See Reference (d) and section 19 of Enclosure 3.

Engaged in research involving human subjects. An institution is engaged in research involving human subjects when its personnel are conducting activities covered by section 219.101(a) of Reference (c) and this Instruction. An institution that is funding, providing equipment, providing access to or information about potential human subjects (but not recruiting human subjects), providing data or specimens (either identifiable or not), or overseeing the research from a regulatory or compliance standpoint is not engaged in the research involving human subjects (but is supporting the research (see "DoD-supported research involving human subjects")).

exempt research involving human subjects. Research involving human subjects where the only involvement of the human subjects in the research will be in one or more of the categories identified in section 219.101(b) of Reference (c).

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

Federal assurance. A written document in which an institution (not an IRB) commits to a Federal department or agency their compliance with the requirements set forth in the Common Rule. Institutions engaged in non-exempt research involving human subjects conducted or supported by the Department of Defense or other Federal departments and agencies that have adopted the Common Rule must have a Federal assurance approved or accepted by the Federal agency supporting the research. The elements of a Federal assurance are outlined in section 219.103(b) of Reference (c).

fetus. The product of conception from implantation until delivery as defined in subpart B of Reference (h).

HRPO. An individual who is delegated the responsibilities as defined in paragraph (a)(2) of section 252.235-7004 of Reference (n). There may be more than one HRPO in a DoD Component. Some DoD Components may use a different title for the person(s) with the defined responsibilities.

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

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

identifiable private information. Defined in section 219.102(f) of Reference (c).

intervention and interaction. An intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between

investigator and subject. See section 219.102(f) of Reference (c) for more information. Examples include, but are not limited to, a physical procedure, a drug, a manipulation of the human subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose, or communication such as a survey or interview.

intramural research. Research (see "research involving human subjects") that is conducted by an entity that is part of the Department of Defense.

institution. An organization or entity defined in a Federal assurance or HRPP.

IO. The senior person authorized to establish and responsible to maintain the HRPP for the institution. Responsible for a Federal assurance and the IRBs internal to the institution, if these elements are part of the HRPP.

(Added)(AF) An IO of an AF institution is its most senior official (e.g., the Commander [General Officer or Senior Executive Service, if present]) with authority to commit the institution to comply with Federal, DoD, and AF requirements.

(Added)(AF) minor. A person who has not attained the legal age of consent to research procedures and is not otherwise legally able to consent.

neonate. Newborns as defined in subpart B of Reference (h).

non-affiliated IRB member. Defined in section 219.107(d) of Reference (c). This member is not connected with the institution(s), as defined in the institution's Federal assurance that is creating or relying on the IRB, or a member of the immediate family of a person who is associated with the institution creating or relying on the IRB.

noncompliance. Failure of a person, group, or institution to act in accordance with this Instruction, its references, or applicable requirements.

non-DoD institution. An entity that is not part of the Department of Defense.

non-exempt research involving human subjects. An activity that meets the definitions of research and human subject but does not meet the criteria where the only involvement of the human subjects in the research are in one or more of the categories identified in section 219.101(b) of Reference (c).

ombudsman. A person who acts as an impartial and objective advocate for human subjects participating in research.

OSD Component. Defined in DoD Instruction 5025.01 (Reference (w)).

OT&E. Defined in section 139(a)(2)(A) of Reference (g).

(Added)(AF) PI. The person responsible for execution of the research and performance of the research team.

prisoner. Defined in subpart C of Reference (h). Includes military personnel in either civilian or military custody or detainment.

prisoner representative. An individual member on the IRB who shall have working knowledge of the human subject population to be recruited, a reasonable familiarity with the operations of the prison or confinement facility, and any other legally imposed restrictive conditions involved in the research, and appropriate background and expertise to serve in this capacity.

private information. Defined in section 219.102(f) of Reference (c).

research. Any activity that is a systematic investigation, including RDT&E, designed to develop or contribute to generalizable knowledge as defined in section 219.102(d) of Reference (c).

research involving human subjects. Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by section 219.101(a) of Reference (c) (including exempt research involving human subjects) and this Instruction.

The following activities conducted or supported by the Department of Defense are NOT research involving human subjects:

Activities carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease in Service members and other mission essential personnel under force health protection programs of the Department of Defense, including health surveillance pursuant to section 1074f of Reference (g) and the use of medical products consistent with DoD Instruction 6200.02 (Reference (x)).

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

Activities performed for the sole purpose of medical quality assurance consistent with section 1102 of Reference (g) and DoDD 6025.13 (Reference (y)).

Activities performed solely for an OT&E project where the activities and project meet the definition of OT&E as defined in section 139(a)(2)(A) of Reference (g).

Activities performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units, including such activities as occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information.

Activities, including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of Government officials responsible for the operation or oversight of the program being evaluated and are not intended for generalized use beyond such program.

Survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by DoDD 5240.01 (Reference (z)).

research involving a human being as an experimental subject. An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of section 980 of Reference (g); it does not affect the application of part 219 of Reference (c). This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of Reference (c), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

research monitor. Individuals with expertise consonant with the nature of risk(s) identified within the research protocol, whose role is to protect the safety and well-being of human subjects.

secretarial designee program. Defined in section 108.3 of Reference (c).

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

(Added)(AF) SGHARP. A panel of experts appointed to routinely provide advice to AFMSA/SGE-C regarding the most ethically and/or scientifically challenging research involving human subjects and/or animal use under AFMSA/SGE-C review per sections 3 and 4 of Enclosure 3.

(Added)(AF) significant change. An amendment to a non-DoD conducted activity that requires prompt notification to HRPO per Enclosure 3, subparagraph 4.b.(4). This includes all substantive changes (see definition below), major non-administrative amendments (e.g., changes in protocol design) and administrative changes that affect HRPO's ability to adequately oversee the activity (e.g., a change in the institution's PI).

(Added)(AF) substantive change. An amendment to an approved item which changes it to the extent it requires new review prior to initiation. Substantive changes are a sub-set of significant changes.

- Examples of substantive changes to AF Issued DoD Assurances requiring AFMSA/SGE-C approval prior to start per paragraph 6.d.(1) of Enclosure 2 include, but are not limited to, changes in signatory officials or in the description of an institution.

- Examples of substantive changes to non-DoD conducted activities requiring HRPO acceptance prior to start per subparagraph 4.c.(2)(c) of Enclosure 3 include, but are not limited to:

-- Addition of any condition identified in paragraph 3.b.(1) of Enclosure 3;

-- Addition of any condition that may impact issues initially reviewed by the HRPO per paragraph 4.c.(2) of Enclosure 3, e.g.:

--- Addition of personnel of institutions not identified upon initial HRPO review;

--- Change in the IRB's determination of review procedure or risk level (e.g., from expedited to exempt, expedited to convened board, etc.);

--- Addition of subjects who cannot consent (see Section 980 of Reference (g)); or

--- Addition of a foreign research site including non-U.S. citizens as human subjects.

UPIRTSO. Any incident, experience, or outcome that meets ALL three of the following conditions:

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.

Is related or possibly related to participation in the research (in this Instruction, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

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.