BY ORDER OF THECOMMANDER
AIR FORCE RESEARCH LABORATORY
(AFRL)

AIR FORCE RESEARCH LABORATORY
INSTRUCTION 40-402

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Medical Command

PROTECTION OF HUMAN SUBJECTS IN RESEARCH

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This instruction describes AFRL procedures for implementing AFPD 40-4, Clinical Investigation and Human Use in Medical Research, and DoDI 3216.02_AFI 40-402, Protection of Human Subjects and Adherence to Ethical Standards in Air Force Supported Research, for research on human subjects conducted or supported by AFRL. It also ensures that AFRL is in compliance with the Code of Federal Regulations (CFR), 32 CFR 219, Protection of Human Subjects. It directs establishment of one or more Institutional Review Boards (IRBs) to provide ethical review of proposed research and oversight of research in progress. This instruction covers all use of human subjects in research, which takes place at AFRL facilities, is conducted by AFRL personnel at any location, or is sponsored or supported by AFRL through contracts or collaborative arrangements. It applies to all AFRL personnel. This publication may be supplemented at any level, but all direct Supplements must be routed to the Office of Primary Responsibility (OPR) of this publication for coordination prior to certification and approval. Refer recommended changes and questions about this publication to the OPR using AF Form 847, Recommendation for Change of Publication; route AF Form 847 through the appropriate functional chain of command. Request for waivers must be processed through command channels to the publication OPR for consideration. Ensure that all records created as a result of processes prescribed in this publication are maintained IAW AFMAN 33-363, Management of Records, and disposed of IAW the Air Force Records Information Management System (AFRIMS) Records Disposition Schedule (RDS).

SUMMARY OF CHANGES

Substantive changes include the following: Department of Defense (DoD-conducted and DoD-supported research better defined; a "DoD addendum" to a Federal-Wide Assurance (FWA) no longer required; Air Force Surgeon General's Human Research Protection Program (HRPP) introduced; roles and responsibilities of Exempt Determination Officials (EDOs) (formerly "review officials") and Human Research Protection Officials (HRPOs) added; clarifies the distinction between Authorized Institutional Official (AIO) and Institutional Official (IO); initiated the requirement for electronic filing of all documents; broadened the scope of monitor duties to those of subject advocacy, rather than limiting research monitoring strictly to medical issues; and updated the DoD-level oversight offices.

1. Applicability and Scope. This instruction covers all research accomplished using human subjects that takes place at AFRL facilities, is conducted by AFRL personnel at any location, or is sponsored or supported by AFRL through contracts or collaborative agreements. Guidance provided in this instruction is in addition to the requirements of 32 CFR 219; 10 USC 980; DoDI 3216.02_AFI 40-402 Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research; where applicable 21 CFR 50, 21 CFR 56 and 45 CFR 46 (subparts B, C, and D) and any other international, federal, state or local requirements applicable to human

research. Where policy is clearly stated in these regulations, it might not be repeated in this instruction.

1.1. **Tests of Materiel.** Research specifically includes the development, test, and evaluation of systems and materiel. Where humans are not the subjects of research, regardless of risk, this instruction will not be applied. Other regulations may apply to these research efforts. Regulation regarding AFRL research test programs is found in AFRLI 61-103, Volume 2, AFRL Test Activity Involving Human Participants, dated 18 June 2014. AFRL directors are responsible for ensuring that any research project involving human subjects is evaluated by the IRB administrative office or a designated EDO IAW DoDI 3216.02_AFI 40-402 to determine if it is human research and subject to IRB oversight.

1.2. **Exempt Research**. Certain types of investigations are exempt from the requirements of formal IRB oversight as described in 32 CFR 219.101. Principal Investigators (PIs) who believe their projects constitute exempt research must have this confirmed in writing by the Air Force Medical Support Agency Research Oversight and Compliance Division (AFMSA/SGE- C), a DoD-Component IRB, the AFRL IRB administrative office, or a designated EDO before data collection begins IAW paragraph 3.6. of this instruction.

1.3. **Collaborative Research.** Studies, which involve collaboration of Air Force investigators with non-Air Force organizations in non-exempt research, must comply with procedures in DoDI 3216.02_AFI 40-402 and other applicable Air Force policies.

1.3.1. DoD/AF-conducted research refers to studies where DoD, AF, or AFRL personnel or AFRL contractors are engaged in actual research activities. "Engaged" is defined as directly interacting with research subjects or having access to personally identifiable information (PII).

1.3.2. DoD/AF-supported research refers to studies where DoD, AF, or AFRL provides non- engaged personnel (e.g., program management), equipment, facilities, funding access to subject populations, etc. For collaborative research efforts conducted by civilian institutions, IRB approval may come from either an Air Force IRB or another IRB whose institution holds an FWA.

1.4. **Human Research Protection Program (HRPP).** The DoD HRPP is a system of interdependent elements that implement policies and practices to protect human subjects involved in research at Component levels. The Air Force Surgeon General (AF/SG) is the Head of the AF Component with delegation of authority to AFMSA/SGE-C.

2. Roles and Responsibilities.

2.1. **AFRL Commander (AFRL/CC).**

2.1.1. Functions as the IO for use of human subjects in research as required by DoDI 3216.02_AFI 40-402.

2.1.2. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol review and approval, to any third party electronically or in written form for any purpose whatsoever.

2.2. **AIO.** The AFRL/CC may delegate IO duties to an AIO per DoDI 3216.02_AFI 40-402.

2.2.1. Oversees AFRL IRB compliance with relevant AF instructions and policies.

2.2.2. Oversees training and continuing education for AFRL IRB administrators, chairpersons, vice chairpersons, and members.

2.2.3. Reviews and approves, approves with conditions, or disapproves IRB-approved protocols.

2.2.4. Appoints and removes the IRB Chairperson and IRB members. Appointments are valid until removal, but subject to an annual review. The chairperson and members will be appointed in writing to include information that position requirements have been fulfilled or are waived by the appropriate authority. Waiver authority is the Air Force Surgeon General's Research and Oversight Division (AFMSA/SGE-C). Letters of removal will state the reason for removal (e.g., permanent change of station, failure to complete membership requirements, misconduct, etc.).

2.2.5. Supervises AFRL IRB administration.

2.2.6. Reviews any reported adverse event involving a human subject involved in research.

2.2.7. Enforces corrective action for any investigators found to be non-compliant with IRB and/or other requirements.

2.2.8. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol review and approval, to any third party electronically or in written form for any purpose whatsoever.

2.3. **IRB.** The purpose of the IRB is to protect the rights and welfare of human research subjects as provided in 21 CFR 50, 21 CFR 56, 32 CFR 219, DoDI 3216.02_AFI 40-402, this instruction, and other applicable regulations, policies, and guidance.

2.3.1. The IRB functions under the authority outlined in 21 CFR 56 and 32 CFR 219. The IRB is established under the authority of the AFRL Commander IAW DoDI 3216.02_AFI 40-402. Oversight of the IRB is provided by the IO/AIO.

2.3.2. The IRB ensures that all research on human subjects conducted or supported by AFRL is accomplished in an ethical manner; that the privacy, comfort, and safety of the subjects are protected to the maximum extent feasible; and that the research is clearly appropriate and fulfills legitimate AF requirements that cannot be met through non-human testing. This requires the IRB to make ethical judgments, as well as assessing the scientific quality or merit of the research design.

2.3.3. The IRB will monitor AFRL investigators for compliance with the requirements for use of human subjects in research mandated by regulations, instructions, policies, and other applicable guidance in paragraph 2.3.

2.3.4. The IRB will ensure that the PIs are aware of AFRL procedures for reporting any adverse event involving a human subject involved in research.

2.3.5. The IRB will conduct required reviews of approved protocols IAW AFPD 40-4 and current guidance from AFMSA/SGE-C.

2.4. **IRB Chairperson**. The IRB Chairperson is the IRB member (see paragraph 2.6.) responsible for the overall operation of the IRB process in terms of ensuring compliance with

applicable regulations and requirements of this instruction. Note: The IRB Chairperson may be dismissed at any time by the IO for failure to fulfill responsibilities or misconduct.

2.4.1. In addition to the requirements in DoDI 3216.02_AFI 40-402, completes initial formal IRB training. This may be a symposium or course sponsored by AFMSA/SGE-C or recognized national agencies (such as IRB 101 and IRB Administrator 101 conducted by Public Responsibility in Medicine and Research (PRIM&R)) and the Collaborative Institutional Training Initiative (CITI) training modules required for IRB members and investigators. Professional IRB certification is encouraged.

2.4.2. Becomes familiar with 32 CFR 219 and DoDI 3216.02_AFI 40-402, as well as this instruction and any other regulations or requirements governing human-subject research.

2.4.3. Ensures that the convened IRB meeting is conducted in a professional manner and that IRB members are given the opportunity to discuss the risks and benefits of research and have their concerns heard in an open and fair environment.

2.4.4. Performs initial review and approval or designates an IRB member to perform an initial review on all protocols submitted to the IRB administrative office.

2.4.5. Reviews and approves IRB meeting minutes.

2.4.6. Signs the final approval letter to investigators for all approved research, unless another authorized designee signs the letter such as a certified EDO.

2.4.7. Recommends to the IO/AIO qualified individuals for IRB appointments.

2.4.7.1. Vice Chairperson(s) may be appointed by the IO/AIO in writing. Any Vice Chairperson must be an IRB member and familiar with the day-to-day operations of the IRB administrative office and may be assigned other IRB-related duties as needed. A Vice Chairperson has the authority to act on behalf of the Chairperson, and must fulfill the responsibilities as delineated for the Chairperson.

2.4.7.2. In the rare event that both the Chairperson and Vice Chairperson are temporarily unable to fulfill their duties, the Chairperson may recommend to the IO/AIO an IRB member as his/her designee on a temporary basis. The IO/AIO's appointment must be in writing, for a specified period of time, and with specific delineation of authorities.

2.4.7.3. IRB members and alternates.

2.4.7.4. EDOs and IRB members who can function as EDOs (see paragraph 2.7.).

2.4.8. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol review and approval, to any third party electronically or in written form for any purpose whatsoever.

2.5. **IRB Administrator.** The IRB administrator is responsible for the day-to-day operation of the IRB administrative office. The administrator should be an expert on HRPP matters, able to assist investigators, the IRB, and leadership in navigating IRB issues.

2.5.1. Completes initial formal IRB training. This may be a symposium or course sponsored by AFMSA/SGE-C or recognized national agencies (such as IRB

Administrator 101 conducted by PRIM&R) and the CITI training modules required for IRB members and investigators.

2.5.2. Becomes familiar with 32 CFR 219 and DoDI 3216.02_AFI 40-402, as well as this instruction and any other regulations or requirements governing human-subject research.

2.5.3. Actively tracks the status of all human research proposals (exempt and non-exempt) submitted to and approved by the IRB. This includes research protocols pending approval, active and ongoing research, and closed research protocols.

2.5.4. Maintains required documentation in an electronic case file for each protocol and exempt request as described in 32 CFR 219.115 and paragraph 3.7. of this instruction.

2.5.5. Ensures the documentation of convened IRB proceedings are in the form of meeting minutes as required in 32 CFR 219.115 (a)(2).

2.5.6. Maintains open communications with each PI on all issues surrounding their research, including but not limited to: courtesy notification to the PI of continuing review, outstanding requirements for review and approval, training requirements, approval notifications, suspension or expiration notifications, and submission of all progress reports throughout the study, the "final report" using the form on the AFRL IRB web site, and copies of any publications or technical reports.

2.5.6.1. Classified Communications. The IR staff should be contacted regarding procedures for communication or submission of any classified information or materials.

2.5.6.2. Communications for Official Use Only (FOUO). Not all communications with IR staff need be FOUO, and it is the responsibility of the sender to comply with applicable regulations, policies, and guidance.

2.5.7. Performs an administrative review of all protocol submissions and ensures that all submission requirements are received before processing for review and approval.

2.5.8. Ensures preparation for the monthly IRB meeting to include: notification of IRB members, distribution of materials to IRB members, notification of investigators with a protocol on the agenda, and reservation and preparation of conference room with audio, visual and computer support.

2.5.9. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol management to any third party electronically or in written form for any purpose whatsoever.

2.6. **IRB Member.** Appointment as an IRB member by the AFRL IO is a voluntary additional duty and a privilege.

2.6.1. Completes required initial and annual training as directed by the IRB chairperson and per IAW DoDI 3216.02_AFI 40-402. (See paragraph 5. of this document.)

2.6.2. Regularly attends and participates in monthly IRB meetings. Members are expected to read all relevant materials prior to each meeting and be prepared to participate in discussion of all issues regarding approval and risk to human subjects.

2.6.3. Declares any conflict of interest and recuses themselves from deliberation and voting when appropriate.

2.6.4. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol review or other action to any third party electronically or in written form for any purpose whatsoever.

2.6.5. Notifies the IRB Administrative Office in writing of their intent to leave the IRB with as much advanced notice as possible and will include the reason for leaving.

2.7. **EDO**. Appointment as an EDO by AFMSA/SGE-C and the IO/AIO is a voluntary additional duty and a privilege.

2.7.1. Completes required initial and annual training as directed by AFMSA/SGE-C and IAW DoDI 3216.02_AFI 40-402. (see paragraph 5 of this document.)

2.7.2. Reviews protocol proposals to determine whether they are exempt or non-exempt IAW 32 CFR 219. EDOs are expected to read all relevant materials prior to making any determination.

2.7.2.1. Documents and maintains records of EDO determinations, including a brief justification for the determination made and a citation to the exempt category, if applicable.

2.7.2.2. Advises the PI of the determination and, if the activity requires IRB approval prior to starting research, refers to the IRB.

2.7.3. Declares any conflict of interest and recuses themselves from deliberation and voting when appropriate

2.7.4. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol review and determination, to any third party electronically or in written form for any purpose whatsoever.

2.7.5. Notifies the IRB administrative office and AFMSA/SGE-C in writing of their intent to no longer serve as an EDO with as much advance notice as possible and will include the reason for leaving.

2.7.6. IRB members may be recommended by the IRB Chair and appointed by the IO/AIO to fulfill the same roles as an EDO as a "IRB Chair Designee" as opposed to an "Exempt Determination Official."

2.8. **HRPO.** AFMSA/SGE-C acts as the Component-level HRPO. An AFRL HRPO exercises written delegation of authority from AFMSA/SGE-C and the IO/AIO.

2.8.1. Completes required initial and annual training as directed by AFMSA/SGE-C and IAW DoDI 3216.02_AFI 40-402. (See paragraph 5. of this document.)

2.8.2. The HRPO reviews non-DoD-institution's HRPP reviews of research protocols for compliance with DoD and AF regulations related to human-subject protections. Prior to the commencement of any research activities, the HRPO must: 1) concur with any non-DoD HRPP determinations prior to start of activities that are either Not Human-Subject Research or Exempt Human-Subject Research prior to start; or 2) approve Non-Exempt Human-Subject Research protocols after any non-DoD IRB approval.

2.8.3. Documents and maintains records of HRPO determinations, including a brief justification for the determination made and a citation to the exempt category, if applicable.

2.8.4. Declares any conflict of interest and recuses themselves from deliberation and voting when appropriate.

2.8.5. Will not disclose or divulge any confidential, proprietary, or private information that is revealed in the course of protocol review and determination to any third party electronically or in written form for any purpose whatsoever.

2.8.6. Notifies the IRB administrative office and AFMSA/SGE-C in writing of their intent to no longer serve as an HRPO with as much advance notice as possible, and will include the reason for leaving.

2.9. **Department/Division Chief.** The chief of each AFRL department or division that conducts or sponsors research on human subjects, or his/her designee at the department/division level or higher, shall assist the IRB administrative office in ensuring compliance by division personnel with this instruction and applicable directives from higher headquarters. The Department/Division Chief:

2.9.1. Ensures that all research with human subjects as defined in 32 CFR 219 is referred to the AFRL IRB for review. No research involving humans may be initiated until either final written approval by the department/division director, or a letter of exemption is obtained from the IRB administrative office.

2.9.2. Reviews all department/division human-subject research protocols prior to submission to the IRB. This review shall address the following:

2.9.2.1. Competence of the principal and associate investigators to carry out the proposed research;

2.9.2.2. Scientific merit of the project as ascertained through appropriate peer review;

2.9.2.3. Relevance of the research to meeting valid AF needs;

2.9.2.4. Necessity for use of human subjects rather than non-human alternatives;

2.9.2.5. Validity of the experimental design including:

2.9.2.5.1. Articulation of a clear and testable hypothesis;

2.9.2.5.2. Establishment of appropriate data quality control;

2.9.2.5.3. Adequacy of planned statistical analysis;

2.9.2.5.4. Appropriateness of number of experimental subjects, sufficient for statistical validity without use of excessive numbers;

2.9.2.5.5. Minimization of discomfort and risk to subjects;

2.9.2.5.6. Adequacy of department/division safety preparedness for medical emergencies, including provision for medical monitoring, procedures for notification of emergency medical personnel, and currency of cardio pulmonary resuscitation or first-aid training of division personnel where applicable; and

2.9.2.5.7. Availability of the required personnel and resources, as well as the

department/ division's intention to implement the protocol if it is approved.

2.9.3. Establishes department/division procedures for review of issues in paragraph 2.9.1, and 2.9.2., above. Departments/divisions will use the IRB-supplied cover letter to document approval of submissions to the IRB.

2.9.3.1. By signing the coordination sheet without exception, the division chief is certifying compliance with all items included in paragraph 2.9.1. and 2.9.2. as required by 32 CFR 219, DoD, and Air Force policy.

2.9.3.1.1. If the protocol fails to meet any criterion in paragraph 2.9.1., 2.9.2., or above, the PI shall attach to the protocol a letter describing the deficiency and justifying the proposal. The Department/Division Chief shall review this narrative and indicate concurrence with the request for IRB review despite the deficiency.

2.9.3.1.2. If the department/division lacks expertise to deal with a specific topic, the Department/Division Chief shall so note on the cover sheet and shall seek appropriate expertise to guide determinations required.

2.9.4. Immediately evaluates reports from investigators or medical monitors concerning any adverse event involving a human subject to determine whether the protocol should be suspended and notifies the IO/AIO and IRB administrative office within 24 hours of such determination. This is in addition to any other management notifications required by local directorate or organizational guidelines or policies. See paragraph 6.3. for additional details regarding IRB and IO/AIO reporting procedures.

2.9.5. Immediately notifies the IRB administrative office of any investigation of scientific misconduct involving an investigator engaged in human-subject research. See paragraph 8. for additional information and reporting procedures.

2.10. **PI.** The PI for each human research protocol has critically important responsibilities as listed in DoDI 3216_AFI 40-402. In addition, the PI must:

2.10.1. Understand and comply with 32 CFR 219, DoDI 3216.02_ AFI 40-402, as well as this instruction and any other regulation or requirement applicable to a specific human-subject research protocol (e.g., 21 CFR 50 Protection of Human Subjects and 21 CFR 56 Institutional Review Boards for Food and Drug Administration (FDA) studies).

2.10.2. Ensure that all human-subject research, whether conducted under an approved protocol or declared exempt, conforms to the terms of its approval or exemption, including any modifications or restrictions imposed during the review process. Unless necessary to eliminate immediate hazards to subjects, changes to approved research will not be implemented until IRB approval is obtained.

2.10.3. Monitor the progress of research and follow AFRL procedures for reporting any adverse event or unanticipated problem involving a human subject.

2.10.4. Maintain current knowledge of related research through review of published literature and contacts with other scientists.

2.10.5. Promptly notify the IRB administrative office if:

2.10.5.1. New information from any source substantially alters the risk/benefit analysis from that represented in the protocol, or if partial results clearly show that continued collection of data is no longer warranted; or

2.10.5.2. Any adverse event or unanticipated problem involving a subject occurs.

2.10.5.3. Any unanticipated risks or other information which might affect the subject's decision to participate in the study.

2.10.6. Provide each subject with a copy of their signed Informed Consent Document (ICD). Subjects may elect to include their ICD in their medical records.

2.10.7. Establish the following records for each approved protocol:

2.10.7.1. IRB-approved protocol and ICD;

2.10.7.2. All approval letters from the IRB and AFMSA/SGE-C (where applicable);

2.10.7.3. Annual progress reports and/or final report;

2.10.7.4. All requested and approved amendments;

2.10.7.5. Adverse events or unanticipated problems;

2.10.7.6. Any Assurance of Compliance approved by AFMSA/SGE-C, and any Individual Investigator Agreements (IIA) when applicable;

2.10.7.7. Copies of the PI and Directorate cover letters; and

2.10.7.8. Electronic/digital versions of the original, signed ICD must be filed with the protocol records. These records must be turned over to the IRB administrator in electronic/digital format for permanent archiving at the time of any progress report and with the final report. The PI may retain the original ICDs in the research file if warranted.

2.10.8. Provide to the IRB Administrative Office an annual listing of scientific publications and presentations relating to each approved human research protocol, including those already terminated.

2.10.9. Notify all interested parties (e.g., Associate Investigators (AIs), Research Monitors, Program managers, Contracting Officers, chain of command, etc.) of any IRB disapproval (see paragraph 3.3.7.2) or suspension or termination (see paragraph 3.10.) of a protocol.

2.10.10. Notify the following of any noncompliance determination (see paragraph 7.) or allegations of misconduct (see paragraph 8.) from any source:

2.10.10.1. AFRL IRB administration;

2.10.10.2. Chain of Command; and

2.10.10.3. Program Manager(s), Contracting Officer(s), and funding agenc(ies) if applicable.

2.10.11. Provide sound justification for waiver of requirements in 21 CFR 50, 32 CFR 219, DoDI 3216.02_AFI 40-402, or this instruction.

2.10.12. Any engaged researcher's failure to comply with responsibilities or requirements may lead to suspension of IRB approval for the protocol until the lapse has been corrected and reinstatement is approved by IRB and the IO/AIO.

3. IRB Procedures.

3.1. **IRB Membership**.

3.1.1. IRB membership will conform to the requirements outlined in 32 CFR 219.107 and DoDI 3216.02_AFI 40-402.

3.1.2. The IRB chairperson along with the IRB administrator will periodically (at least annually, but as often as necessary) review IRB membership regarding the recruitment, retention, or dismissal of members. This review includes examination of attendance, specialty, expertise, education, affiliation, and diversity. Following this review, the IRB Chairperson recommends appointments or dismissals to the IO/AIO.

3.1.3. The IO/AIO will formally appoint or dismiss members in writing.

3.1.4. There is no specific term (length) of appointment. The IRB membership will be reviewed at least annually and adjusted as appropriate.

3.1.5. Appointment as an IRB member is a privilege, not an entitlement. An IRB member may be dismissed at any time for failure to fulfill responsibilities delineated in this instruction or for misconduct.

3.1.6. The IRB may call upon outside consultants as necessary for additional expertise on a particular population or area of research. Outside consultants are not voting members, but are expected to maintain the confidentiality of the research.

3.2. **IRB Meetings**.

3.2.1. Schedule. A convened IRB meeting will be held at least once per month for review of research that does not qualify for exemption or expedited review. The submission deadline for review at an IRB meeting is three weeks prior to the date of the meeting. All submission requirements must be received by this date in order for a protocol to be considered at the meeting. Off-schedule meetings may be convened to address urgent issues. Convening an off- schedule meeting depends entirely on the schedule of IRB members and the ability to obtain a quorum.

3.2.2. Agenda. The IRB Chairperson may bring any issue to the convened IRB meeting, which he/she deems appropriate for consideration and voting. In addition to the review of new and continuing research protocols, the agenda will include a monthly training topic, a quality assurance (QA) section, research that was reviewed and considered to be exempt, a list of research approved through expedited procedures, adverse events, and noncompliance or misconduct issues.

3.2.3. Voting. A period of discussion and the voting of IRB members are conducted without the investigators in attendance. Investigators never participate in the voting process. Voting will follow a formal motion, which has been followed through with a second. If there is no second to a motion, there will be no vote and the motion will not be further considered. Votes will be tallied by a show of hands [or statement of the word "aye" to agree or the word "nay" to disagree] with the motion at hand. All those in favor,

opposed, and abstaining from voting will be recorded. A motion will be considered approved if it receives a simple majority of votes in favor of approval.

3.2.3.1. Opposing Positions. The reasons for individual members voting against a motion (opposed) must be documented in the minutes.

3.2.3.2. Abstentions. Although all members with an opinion on a motion should register a vote, they cannot be compelled to do so. A member may choose to abstain for any reason, such as where the member feels uncomfortable voting for or against a motion. Note that an abstention may count as a vote against a motion.

3.2.3.3. Recusals. Any IRB member with a conflict of interest is recused from the discussion and voting process and must leave the room for the final discussion and vote (see paragraph 12. of this instruction). When a member is recused from discussion and voting on a protocol, that person does not count in the tally of voting members present towards a quorum for that protocol. In the event that a recusal should reduce the number of members present to below a quorum, the IRB may still discuss a protocol, but may not vote to approve it; the protocol will be automatically tabled until the next IRB meeting for voting.

3.3. **Initial Review**. A new protocol submitted to the IRB administrative office for review will follow the review sequence outlined below. A submission will not be considered complete until the IRB has received all of the required items specified in paragraph **3.3.1**

3.3.1. Submission requirements. The following items are required for each protocol submitted to the IRB administrative office and must conform to the format and instructions provided for each document. Current templates and instructions for completing these forms can be found on the IRB web site or obtained from the IRB administrator. Once these items are received, the protocol will be considered for review and approval.

3.3.1.1. Signed Directorate Cover Letter (DCL);

3.3.1.1.1. The DCL may take place of the division cover letter if the division is one of the signatures on the DCL. The DCL shall act as the requisite scientific review required of a new protocol being submitted to the IRB.

3.3.1.2. Signed PI cover letter;

3.3.1.3. Research protocol;

3.3.1.4. Informed Consent Document (ICD);

3.3.1.5. Assurance of Compliance;

3.3.1.6. Proof of completed human-subject research protection training per paragraph 5.2. of this instruction is required for all investigators and key research personnel; and

3.3.1.7. Curriculum vitae for investigators, which has been dated within one year of submission.

3.3.2. Administrative review. All proposals submitted to the IRB administrative office will be reviewed first by an IRB administrator to ensure that the protocol, ICD, and all required supporting documentation are complete. Once administrative review is

complete, the IRB administrator will forward the protocol and pertinent supporting documents to the IRB chairperson or designee for review.

3.3.3. Primary review. The IRB Chairperson or designee will conduct the initial review of all protocols. This review will consist of the following determinations:

3.3.3.1. Human-subject research definitions. A determination is made if the proposal consists of human research based on the definitions provided in 32 CFR 219.102 (d) & (f), as well as DoDI 3216.02_AFI 40-402. If a protocol or activity is determined to be research that does not involve human subjects or is not research at all, a written determination will be provided to the PI that includes an explanation as to why the proposal does not meet the defined criteria for human-subject research. No further IRB review or oversight will ensue for projects that are determined not to be human-subject research.

3.3.3.2. Risk level. The risk to subjects for participation in human-subject research is evaluated based on the procedures involved and the definition of risk provided in 32 CFR 219.102 (i). If there is any question that a protocol may be greater than minimal risk, it will be scheduled for review at a convened IRB meeting.

3.3.3.3. Review category. One of three review categories will be assigned: exempt, expedited, or convened IRB review. If the protocol is deemed minimal risk by the reviewer, a determination will be made if it may be exempt or reviewed through expedited review procedures. Even though the protocol may qualify for exemption or expedited review, the reviewer may assign a higher level of review (expedited or convened IRB, respectively) if he/she deems necessary.

3.3.3.3.1. See paragraph **3.6**. of this instruction, Exempt Research, for details regarding the Exempt review category.

3.3.3.3.2. Expedited review. If the research falls into one or more of the categories of expedited review designated by the Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP) and meets the criteria in 32 CFR 219.110, it may be processed by expedited-review procedures. The IRB Chairperson or appoint an IRB member to conduct expedited review. The reviewer may exercise all of the authorities of the IRB, except for recommendation for disapproval. Following initial review of the protocol, the reviewer will communicate concerns and/or conditions of approval to the PI. The PI will respond with a revised protocol and explanation or clarification of any issues of concern raised by the reviewer. The reviewer may refuse to approve a protocol through expedited procedures if he/she feels that the PI is not adequately addressing concerns or refuses to comply with conditions of approval. The reviewer may exercise all of the authorities of the IRB, except for recommendation for disapproval. In this case, the research will be referred to the convened IRB for consideration. The date the IRB Chairperson or designee signs the IRB approval letter is the official approval date for an expedited protocol.

3.3.3.3.3. Convened IRB review. If the protocol is not exempt and does not meet the criteria for expedited review, it will be scheduled for review at the next convened IRB meeting IAW the deadlines in paragraph 3.2.1. of this instruction.

3.3.3.4. When a protocol is brought to a convened meeting, the IRB will:

3.3.3.4.1. Determine if the research involves minimal or greater than minimal risk to subjects.

3.3.3.4.2. Determine the frequency of continuing review to be conducted on at least an annual basis. The IRB may determine that continuing review should be earlier than one year based on specific risks to subjects or circumstances of the research involved.

3.3.3.4.3. Approve, approve with conditions, table for another meeting, or disapprove reviewed protocols for another meeting. The date of the IRB meeting at which the protocol is approved or approved or approved with conditions will be the official approval date of a full-board protocol.

3.3.3.4.3.1. Approved means accepted as written with no conditions.

3.3.3.4.3.2. Approved with conditions means the protocol is approved pending explicit minor changes. All explicit conditions requested must be completed and documented before final IRB approval will be released. For these conditions, the IRB Chairperson or other IRB member present can, upon reviewing the PI's response(s) to the conditions, approve the research on behalf of the IRB with the IRB membership's concurrence by vote to do so.

3.3.3.4.3.3. Tabled means that no voting occurs, and the protocol is delayed until a future meeting pending changes. Generally, the protocol, ICD, or other materials have deficiencies that prevent accurate determination of risks and benefits, or require significant clarifications, modifications or conditions that, when met or addressed, require convened IRB review and approval of the PI's responses and revisions.

3.3.3.4.3.4. Disapproved means that as proposed, the protocol describes a research activity that is deemed to have risks which outweigh potential benefits, protocol is significantly deficient in several major areas, or otherwise does not comply with applicable requirements referenced in paragraph 1. of this instruction. Investigators will be notified in writing of disapproval, the reason(s) for disapproval, and provide instructions for how to appeal the determination. A protocol that is disapproved may be resubmitted if the protocol is revised to address all reasons for IRB disapproval.

3.3.4. Legal consultation and review. A legal officer will serve as a consultant to the convened IRB, and in this capacity will have visibility on and provide consultative input to all IRB agenda items. Formal written legal review will be obtained for all initial non-exempt research protocols in the following categories:

3.3.4.1. Research deemed to be greater than minimal risk;

3.3.4.2. Research involving weapons;

3.3.4.3. Research involving vulnerable or special populations as subjects (e.g., pregnant women, fetuses, neonates, children, prisoners, detainees, and mentally or physically handicapped);

3.3.4.4. Any other protocol for which Component-level review would be required prior to initiation of research; or

3.3.4.5. Any protocol for which legal review is requested.

3.3.5. Institutional review. Once the protocol has been approved through expedited review or by the convened IRB, it is forwarded to the IO/AIO for review and determination IAW paragraph 2.2.3. The IO/AIO receives a letter of approval from the IRB Chairperson or designee for expedited protocols or a copy of the meeting minutes for protocols approved at the convened meeting. Initial non-exempt research may not begin until the PI is notified of IO/AIO and, under some conditions, AFMSA/SGE-C (see paragraphs 3.3.6.3. and 3.3.6.4.) concurrence with IRB approval.

3.3.6. AFMSA/SGE-C review. After institutional review and approval, all non-exempt research is forwarded to AFMSA/SGE-C for review.

3.3.6.1. Written approval of exempt status by a designated EDO, IRB Chair, or convened IRB will enable research to proceed concurrently with AFMSA/SGE-C review.

3.3.6.2. If the protocol is approved as minimal risk through expedited review procedures or convened IRB meeting, research may proceed concurrently with AFMSA/SGE-C review.

3.3.6.3. If the protocol is approved as greater-than-minimal risk by the IRB or requires an Assurance of Compliance to be issued by AFMSA/SGE-C, final approval will not be issued to the PI until AFMSA/SGE-C review is complete.

3.3.6.4. In addition, all international research, regardless of exemption status, will be forwarded to AFMSA/SGE-C for review and approval prior to final approval being issued.

3.3.7. Final approval/disapproval. Final approval of research is issued to the PI in writing only after all of the above steps have been completed.

3.3.7.1. Final written approval will include a statement that requires the investigator to obtain IRB approval before implementing changes and report adverse or unanticipated events to the IRB administrative office. The final approval will also include the date of IRB approval, the date at which IRB approval will expire, and the date continuing review will be due.

3.3.7.2. If proposed research is disapproved either by the IRB or IO/AIO, the PI will be notified in writing to include an explanation as to why the research was not approved.

3.4. **Continuing Review**. Unless determined otherwise by the IRB, all approvals are valid for the period not to exceed one year. This is determined from the date of approval (date of the meeting at which a protocol was approved by the convened IRB or the date the approval letter to the IO/AIO is signed by the IRB for expedited review). The IRB does not have authority to extend the term of approval for each protocol beyond one year under any condition. The date upon which a protocol approval term ends is referred to as the expiration date.

3.4.1. Frequency of review. A determination will be made upon initial IRB approval regarding the appropriate term of approval for each protocol. Per 32 CFR 219, continuing review must be accomplished on at least an annual basis. In order to ensure continuing review is conducted at least on an annual basis, renewal requests will generally be due 11 months from the date of IRB approval unless otherwise specified by the IRB. A progress report, (see AFRL IRB web site for the template), electronic/digital of original signed ICDs (the PI may retain the original copy for their research records), and an amended research protocol (if amendments are requested) must be turned in to the IRB administrative office 30 days prior to the date for continuing review indicated on IRB approval letter. For example, a protocol initially approved on 3 January 2014 for a term of one year would be scheduled for IRB review in December 2014, and the progress report would be due to the IRB on 3 November 2014; the IRB approval of the study would expire on 2 January 2015 if continuing review had not been performed. Though the IRB administrative office sends PIs courtesy notifications of impending review and expiration of protocols, it is ultimately the responsibility of each PI to ensure required documentation is submitted to the IRB in a timely manner.

3.4.2. Expiration of IRB approval. If IRB approval of continuing review is not completed within the term of approval set by the IRB, the protocol will expire. The IRB administrative office will issue a letter notifying the PI of the expiration and instructing that all human research activities must be halted until the research can be reviewed and approved. A non-compliance inquiry may be conducted for protocols not submitted before expiration.

3.4.3. Compliance verification. The IRB may require verification outside that of the investigator that no changes have occurred in the protocol since the previous IRB review. For example, this may be accomplished for protocols where the investigator has had the current or other protocols suspended for non-compliance in the past year.

3.5. **Amendments**. Any change to a research protocol or the ICD must be submitted to the IRB administrative office as a written request. The amendment request must follow the established format (see AFRL IRB web site for the template) and include any revised or new study documents (e.g., protocol, ICD, recruitment materiel, etc.) with all changes marked. Amendments must be made to the most current version of the protocol in tracked changed edits, so that changes to the protocol are readily identifiable. No change to a protocol or ICD may be implemented without prior IRB approval.

3.5.1. Minor changes to previously approved documents during the period (of one year or less) for which approval was previously authorized may be reviewed and approved by the IRB Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the IRB.

3.5.2. Changes that are considered more than minor may be reviewed and approved by the IRB Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the IRB if the modified version represents minimal risk and otherwise falls into one or more of the categories of expedited review designated by the OHRP (see paragraph 3.3.3.3.2.).

3.6. **Exempt Research**. Each proposal submitted to the IRB administrative office will be considered for exemption whether submitted as a specific exempt request or as a full research

protocol. If a full research protocol qualifies for exemption, the PI will be notified and given the opportunity to pursue exemption if they so desire. If a request for exemption is denied, the PI will be notified in writing, and given the opportunity to pursue expedited or convened-board review.

3.6.1. Submission requirements. Research activities that may be categorized as exempt IAW 32 CFR 219.101(b) can be submitted to the IRB using an exemption request (see AFRL IRB web site for the template). In addition to the completed exemption-request template, the following are required before submission of an exemption request:

3.6.1.1. Completion of AFRL human-subject protections training is required for all investigators per paragraph 5.2. of this instruction.

3.6.1.2. A DCL must be included if the research is being conducted or sponsored by AFRL.

3.6.1.3. If the proposal involves international research, a letter of exemption from an IRB in the country where the research is to be executed must be submitted. This letter must specifically state that the proposed research is considered exempt or not normally subject to IRB or regulatory oversight by local laws and standards.

3.6.2. Each exemption request will be reviewed by the IRB Chairperson or designee. A written determination will be provided to the investigator stating whether or not the proposed activity is exempt.

3.7. **Records**. The IRB administrator will maintain a case file for each protocol or exempt request submitted to the IRB administrative office. These records will be retained indefinitely. Each case file will include:

3.7.1. IRB approved protocol and ICD;

3.7.2. All approval letters from the IRB, IO/AIO, and AFMSA/SGE-C (where applicable);

3.7.3. Annual progress reports and a final report;

3.7.4. All requested and approved amendments;

3.7.5. Adverse events or unanticipated problems;

3.7.6. All substantial correspondence between the PI and the IRB administrative office;

3.7.7. IRB minutes for the meeting where the research was reviewed/approved;

3.7.8. Any Assurance of Compliance approved by AFMSA/SGE-C or an individual investigator assurance where applicable;

3.7.9. Documentation of legal review (where applicable);

3.7.10. Directorate and PI cover letters;

3.7.11. Curriculum vitae of investigators;

3.7.12. Digital copies of all ICDs signed by all subjects;

3.7.13. Presentations or publications resulting from the research submitted by the PI; and

3.7.14. Investigations of non-compliance to include final outcome.

3.8. **Appeal of an IRB decision**. A PI has the right to appeal any decision made by the IRB. Appeal of an IRB decision must follow the procedures outlined below.

3.8.1. The appeal must be for the IRB to reconsider a decision.

3.8.2. The decision must be opinion-based (does not violate law/regulations).

3.8.3. The appeal is made in writing within 30 days of written notification of the IRB's decision.

3.8.4. The appeal will be reviewed by the IRB. The IRB will invite the investigator to the IRB meeting if the IRB has additional questions for the investigator. The IRB will reconsider its decision. The following actions are available: 1) let the previous decision stand; or 2) reverse all or part of the previous decision.

3.8.5. In accordance with 32 CFR 219.112: "Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB." Therefore, any second decision by the IRB is final.

3.9. **Protocol Closure.** When human subjects research under an approved protocol is complete, a final report is required to close the protocol. Research under a particular protocol is considered to be complete when the study is closed to the enrollment of new subjects and all data collection and analysis of PII data are complete.

3.9.1. A study cannot be closed by the IRB administrative office without a report from the PI confirming that research is complete and there is no further interaction with human subjects or PII data.

3.9.2. All electronic/digital versions of the originals of any signed ICDs not previously turned in at the time of the last continuing review (if any) must also be submitted to the IRB at the time of the protocol closure request.

3.9.3. If a protocol is reviewed but never fully approved, a final report is not required.

3.10. **Suspension or Termination of IRB Approval.** Previously approved research may be suspended for concerns regarding subject safety or welfare, potentially serious or continuous non-compliance, or expiration of approval.

3.10.1. Immediate suspension of research activities for any reason other than expiration of initial approval or continuing review (see paragraphs 2.5.6, 3.3.7.1, and 3.4.) may be made by the IRB Chairperson, IO/AIO, or chain of command.

3.10.2. Continued suspension or any termination of IRB approval for research must be made by the convened IRB or IO/AIO. Written notification with reason(s) stated must be made to the PI, Department/Division Chief, IO/AIO, and AFMSA/SGE-C.

3.10.3. Although IRB approval of research can only be terminated by the convened IRB or IO/AIO, the chain of command can suspend or terminate support of research activities when investigators or the institution has materially failed to comply with the approved protocol or failed to discharge responsibilities for the protection of the rights and welfare of human research subjects. Written notification with reason(s) stated must be made to

the PI, Department/Division Chief, and IRB Chairperson. The IRB Chairperson will notify the IO/AIO and AFMSA/SGE-C.

4. Additional Oversight of Research Protocols. Research oversight of protocols is provided by one or more qualified individuals IAW DoDI 3216.02_AFI 40-402, Enclosure 3, Section 8, and this instruction. All greater-than-minimal-risk research must have at least one research monitor, who is sufficiently removed from the research at hand to provide objective analysis and oversight of research risks. The PI and Research Monitor have the responsibility for suggesting the level of oversight needed for a specific protocol. Research consultant(s), research monitor(s), and research observer(s) may be employed for this purpose. The IRB will ensure that each is appropriately qualified to serve in such a capacity based on the nature of the research and the characteristics of risks involved. The IRB has responsibility to determine what level of oversight will occur. Definitions and responsibilities for different types of research oversight are provided below. Individuals may serve more than one role, as long as constraints defined below are not violated.

4.1. **Research Consultants.** The primary oversight role a research consultant plays is advising the PI and Department/Division Chief during protocol development in areas or on issues requiring specialty expertise. That special knowledge and experience may be administrative, scientific or technical, medical or nonmedical, or any other expertise not intrinsic to the research team.

4.1.1. The department/division originating the protocol must obtain appropriate research-consultant review and approval before the protocol is submitted to the IRB. That this review occurred is documented in the DCL and shall:

4.1.1.1. Determine, along with the PI, what risks and discomforts are anticipated in the research. The risks and discomforts may be physical, psychological, potential breach of confidentiality, or other.

4.1.1.2. Assure that protocol design minimizes risk, discomfort, and psychological stress to subjects, and that appropriate provisions are made for protection of privacy and confidentiality. Where a Health Insurance Portability and Accountability Act of 1996 (HIPAA) covered entity is involved, ensures that permission for release or the appropriate HIPAA waiver is obtained.

4.1.1.3. Determine that the protocol specifies appropriate medical procedures to screen out potential subjects with preexisting conditions or pathology that would result in greater than expected risks.

4.1.1.4. Assure that department/division equipment, procedures, training, and personnel are adequately prepared to meet any medical emergency that might occur during research involving human subjects.

4.1.2. Any medical research consultant will be credentialed or licensed as appropriate to the medical risks involved in the research.

4.1.3. An appropriately qualified research consultant may also be designated for additional duties during conduct of the research (e.g., providing medical screening of prospective participants prior to enrollment or prior to each intervention, research observation, standing by for intervention in case of an adverse event, etc.).

4.1.3.1. Any interaction or intervention with human subjects or access to subjects' PII or PHI would engage the research consultant in conduct of the research, thus disqualifying that research consultant from also serving as a research monitor (see paragraph 4.2.2.).

4.1.3.2. Research consultants employed after research initiation must be approved by the IRB.

4.2. **Research Monitors.** The primary oversight role a research monitor plays is that of subject advocacy throughout protocol development and during conduct of the research. Research Monitors will have the knowledge, skills, and abilities necessary to appropriately monitor the research being conducted consonant with the nature of the risk(s). There may be more than one Research Monitor if different skills or experiences are necessary for different aspects of the research, though one must be designated as the research monitor with overall responsibility for subject advocacy and interface with the IRB.

4.2.1. All greater-than-minimal-risk research must have at least one research monitor. Some minimal-risk research may have one or more Research Monitors designated by the PI, IRB, or IO/AIO.

4.2.2. At all times, research monitors shall be independent of the team conducting the research involving human subjects. In this context, "independent" is defined as not involved in collecting data through intervention or interaction with the individual or obtaining, or having access to PII or Protected Health Information (PHI) except in emergencies. If a Research Monitor fulfills other duties (e.g., research consultant or research observer), protocol documents must separate the Research Monitor duties and any other duties the same individual may be performing.

4.2.3. In addition to complying with all stipulations and executing all responsibilities detailed in DoDI 3216.02_AFI 40-402, Enclosure 3, Section 8; the duties of a Research Monitor include:

4.2.3.1. Determining, with the concurrence of the IRB, the level of on-site research observation that is required for the level and type of risk(s). Depending on the nature of the risks involved during the experiment, a research observer may be required to be on call, in the same building, or continuously present and in communication with the subject.

4.2.3.2. If research requires on-scene observation, and the research monitor is not required to personally provide this observation, but the research monitor is responsible to design an appropriate system to provide observation, and with the IRB must concur/approve. This includes selection and training of any research observer.

4.2.3.3. Ensuring a mechanism exists that informs subjects of the advocacy role of research monitors and delineates a process by which subjects may contact the overall Research Monitor should they desire to do so.

4.2.3.4. Reporting to the IRB and Department/Division Chief any adverse event involving a subject. Any research/ consultant should assist in determining actual or potential harm. The report should include the research monitor's recommendation as

to whether or not the protocol should be stopped pending further investigation or until the IRB can access the research monitor's report.

4.2.4. Any medical research consultant will be credentialed or licensed as appropriate to the medical risks involved in the research.

4.3. **Research Observers**. The primary oversight role of a research observer is to personally witness research conduct for the purposes of interceding should an adverse event occur. Although the PI bears overall responsibility for subject safety and the research monitor bears overall responsibility for subject advocacy, neither is required to personally oversee data-collection sessions, unless such is determined by the IRB, but either may appoint one or more qualified research observers to directly monitor subject safety during data collection or other intervention.

4.3.1. Depending on the nature of the research, it may be appropriate for the research observer to be on call instead of physically present. However, research observers are employed must be approved by the IRB.

4.3.2. Research observers may participate in other aspects of the research; however, they must be focused on subject safety, and post-intervention assessment when applicable, while serving in the observer role.

4.3.2.1. A research consultant may serve as an on-site research observer consistent with paragraph 4.1.3.

4.3.2.2. A research monitor may serve as an on-site research observer, except as noted in paragraph 4.2.2.

4.3.3. The duties of a research observer include:

4.3.3.1. Immediate termination of any experiment if it appears that the subject is at increased risk for any reason (e.g., if the subject's vital signs physiological or psychological stress exceeds acceptable levels, if a subject may fall or an object may fall on a subject, if a piece of equipment appears to not be functioning properly, etc.); and

4.3.3.2. Providing first response to any adverse event involving the subject, research team, or bystanders.

4.3.4. Any medical research observer will be credentialed or licensed as appropriate to the medical risks involved in the research.

5. HRPP

5.1. **Applicability.** All investigators and key personnel involved in the conduct of human-subject research (exempt or non-exempt) are required to complete, with a passing score, HRPP training prior to submitting a protocol or exempt request to the IRB administrative office.

5.2. **Training for Personnel Engaged in Human-Subject Research**. Both initial and recurrent training for investigators and other engaged personnel will consist of the designated AFRL modules on the CITI web site or other training modules approved by the AFRL IRB. Failure of any investigator or key personnel to complete initial and recurrent training may result in suspension of IRB approval for all protocols in which the individual is engaged.

5.2.1. DoD personnel and non-DoD personnel acting under the FWA issued to AFRL are required to complete training prior to one year from the date of the previous training.

5.2.2. Non-DoD personnel acting under a non-DoD Assurance are required to complete training prior to three years from the date of the previous training.

5.3. **Continuing Education for IRB Members.** A continuing education topic for IRB staff and members will be included as standard agenda for each IRB meeting. The nature and content of this training is at the discretion of the IRB chairperson.

5.4. **Training for Institutional Officials, IRB Members, and HRPP Staff**. Training for IO/AIOs, IRB members, and HRPP staff will consist of initial and annual completion of the required AFRL modules on the CITI web site or other training modules approved by the AFRL IRB. Additional training requirements are listed under "Roles and Responsibilities" for respective positions.

6. Adverse Events and Unanticipated Problems. Research should be designed in such a way as to minimize the occurrence of adverse events. However, adverse events and unanticipated problems that involve risk to subjects or others may arise. It is crucial that investigators and research monitors take the appropriate steps in evaluating and reporting any adverse event or unanticipated problem. While the research monitor should be closely involved, it is ultimately the responsibility of the PI to report adverse events and take the appropriate corrective action.

6.1. **Adverse Events**. An adverse event is any untoward or unfavorable medical occurrence (physical or psychological) in a human subject, including any abnormal sign (e.g., abnormal physical examination or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. There are several types of adverse events defined in DoDI 3216.02_AFI 40-402.

6.1.1. Serious adverse events. A serious adverse event results in death, threat to life, limb or eyesight, inpatient hospitalization (or prolongation thereof), persistent or significant disability/incapacity, a congenital anomaly or any event that may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

6.1.2. Unexpected adverse events. Any untoward experience not identified in the risks and discomforts section of the protocol and ICD.

6.1.3. Important medical events. An important medical event is an incident, experience, or outcome that is neither serious nor unexpected, but may have an impact on risk to subjects or others and warrants evaluation and reporting.

6.2. **Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO).** An unanticipated problem may not meet the criteria for an adverse event. An unanticipated problem is any incident, experience, or outcome that meets all of the following criteria:

6.2.1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and ICD; and (b) the characteristics of the subject population being studied;

6.2.2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

6.2.3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.3. **Reporting of Adverse Events and Unanticipated Problems.** All reports of adverse events or unanticipated problems must follow the established format and be submitted in writing. Reports from the IRB to the IO/AIO and AFMSA/SGE-C may be included in the meeting minutes with the attached report from the PI.

6.3.1. The PI must report any adverse event that is both serious and unexpected to the IRB as soon as possible but within 72 hours from the time the event is recognized.

6.3.2. The PI must report any unanticipated problems to the IRB as soon as possible, but at least within seven working days of recognition.

6.3.3. All adverse event reports will be reviewed at the convened IRB meeting. The IRB will either accept the report as submitted, request additional information or require additional corrective actions to be taken, to include suspension or termination of IRB approval. The IRB may also request a follow-up report at a specified interval. If approval of the protocol has already been suspended or research temporarily halted, the IRB will determine if, and under what conditions or modifications, the research may resume. Documentation of the review will be recorded in the IRB Meeting Minutes.

6.3.4. The IO/AIO will be notified of all adverse events and unanticipated problems in the IRB meeting minutes.

6.3.5. The IRB must report any adverse event that is both serious and unanticipated to AFMSA/SGE-C as soon as possible but within 15 working days of notification.

6.3.6. PIs may be required to notify the Department/Division Chief IAW paragraph 2.9.4 of this instruction, management IAW local directorate or organizational guidelines or policies, or other agencies of adverse events or unanticipated problems, so subsequent reporting and investigation can be conducted (e.g., Detachment Safety Office IAW AFI 91-204, paragraph 2.7.5 for military and 2.7.6 for civilian, etc.). Timelines for these reporting requirements may vary from IRB requirements. Investigators are responsible to ensure they know and adhere to these requirements.

7. Non-compliance. Non-compliance is different from scientific misconduct which is addressed in paragraph 8. of this instruction. Non-compliance may be intentional or unintentional. All allegations of non-compliance are taken very seriously and will be investigated in a fair, thorough, and objective manner with every effort to maintain the confidentiality of those involved.

7.1. **Definitions**.

7.1.1. Non-compliance is any violation of any regulation that governs human subject research or the failure on the part of any investigator conducting human research to

comply with the requirements of the IRB or any deviation from the study documents (e.g., protocol, ICD, recruiting material, etc.) approved by the IRB.

7.1.2. Minor non-compliance does not impact in a significant manner subject safety, compromise the integrity of the study or data, violate a subject's rights or welfare, or affect the subject's willingness to participate in the research, and there is no recognized harm to subjects.

7.1.3. Serious non-compliance may impact in a significant manner subject safety, compromise the integrity of the study or data, violate a subject's rights or welfare, or affect the subject's willingness to participate in the research.

7.1.4. Continuing non-compliance is a series of more than one non-compliant event, in reasonably temporal proximity that indicates the need for evaluation of methods and systems used to protect human subjects.

7.2. **Initial Investigation**. All allegations of non-compliance in human research will be initially reviewed and investigated by the IRB chairperson. The IRB chairperson will determine if there was minor, serious, or continuous non-compliance involved. The IRB chairperson may refer any case of alleged non-compliance to the IRB for any reason. If at any point during the investigation of non-compliance it appears that scientific misconduct may also be present, procedures in paragraph 8 of this instruction will be followed.

7.3. **Referral to the IRB.** If the IRB chairperson determines that the non-compliance is potentially serious or continuing, the case will be referred to the convened IRB. The IRB will review the facts gathered by the IRB chairperson and any information submitted by the investigator. The investigator will be offered the opportunity to speak to IRB members at the meeting to present any information in person. The IRB will then determine the nature of non- compliance and agree upon a corrective action.

7.4. **Notification of Action**.

7.4.1. Minor non-compliance. If the IRB chairperson determines that minor non-compliance is involved, the PI and the PI's chain of command or line of reporting will be notified in writing. Written notification will describe the nature of the non-compliance and include any corrective action that is required.

7.4.2. Serious or continuous non-compliance. In addition to notifications in paragraph 7.4.1, the IO/AIO and AFMSA/SGE-C will be promptly notified upon initial determination. The IO/AIO will consider the recommendation and decide on an appropriate course of action. Following IO/AIO disposition, the PI along with his/her branch and Department/Division Chiefs will be notified in writing of the corrective action.

7.5. **Appeals.** Appeals may be made IAW paragraph **3.8** of this instruction.

7.6. **Records.** All records regarding the investigation of non-compliance, including facts gathered, correspondence, IRB minutes, letters to the investigators, and notification letters to others (e.g., chain of command or line of reporting, IO/AIO, AFMSA/SGE-C, etc.) will be filed in the corresponding protocol case file.

8. Scientific Misconduct. Scientific misconduct is defined in DoDI 3216.02_AFI 40-402 as the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in

reporting research results. All allegations of scientific misconduct will be investigated and resolved IAW DoDI 3210.7 Research Integrity and Misconduct and DoDI 3216.02_AFI 40-402. The additional procedures outlined below apply only if the alleged misconduct involves human research. All allegations of scientific misconduct are taken very seriously and will be investigated in a fair, thorough, and objective manner with every effort to maintain the confidentiality of those involved.

8.1. **IRB Chairperson Responsibilities.** If the potential for scientific misconduct arises during an investigation of non-compliance, the IRB chairperson will immediately notify the Department/Division Chief of the investigator(s) involved.

8.2. **Department/Division Chief Responsibilities**. The Department/Division Chief will notify the IRB chairperson immediately if, following an inquiry, an investigation of scientific misconduct is initiated on an investigator. The Department/Division Chief has the responsibility to notify the Directorate Commander or Director, depending on organizational structure and processes.

8.3. **Determination of Violations**. The IRB chairperson will assist the Department/Division Chief in determining if human research subject rights were violated or harm to subjects resulted from the misconduct.

8.3.1. If the IRB chairperson determines that subjects were harmed or their rights were violated as a result of the misconduct, the case will be referred to the IRB for consideration.

8.3.2. If the IRB chairperson determines that subjects were not harmed and their rights were not violated, this will be documented in writing to the Department/Division Chief and the investigator may continue research IAW 711 HPW OI 61-01 *Research Ethics within the 711th Human Performance Wing*.

8.4. **Review of Alleged Scientific Misconduct.** IRB review of alleged scientific misconduct will follow the same procedures outlined for alleged cases of non-compliance in paragraphs 7.3. thru 7.6. of this instruction. Any corrective action imposed by the IRB will be in addition to any requirements following the investigation conducted under procedures in 711 HPW OI 61-01.

9. International Research. International research is defined as research that is conducted at a facility outside of the continental United States and involves research subjects that are not U.S. citizens. In addition to the standard submission requirements, international research will require review by an IRB or other ethics committee that reviews human research in the local community of the country in which the research is to be conducted. Whenever possible, this committee should satisfy the IRB membership requirements outlined in 32 CFR 219.107. This IRB or ethics committee must be able to review the research and ensure that it is acceptable based on national and local requirements, standards, and norms. This committee must also be willing to serve in an oversight capacity to assist the AFRL IRB in any matters of compliance and oversight. The AFRL IRB must be provided with the informed consent documents in the native language, as well as a back-translated version for review. All international research, regardless of risk level or determination of exemption, must be reviewed and approved by AFMSA/SGE-C prior to research commencement.

10. Quality Assurance (QA). The IRB administrative office will conduct random audits of approved research to ensure compliance and look for opportunities for quality improvement (QI). A roster of all audits and any findings will be reviewed at the next convened IRB meeting.

10.1. **External**. External audits refer to those reviewing research activities. These may be random as part of an ongoing QA/QI program; grouped by individual or organization, approval category, risk level, or study parameter; triggered by an incident such as change in risk level, adverse event, allegation (e.g., conflict of interest, non-compliance, misconduct, etc.), or subject complaint; or other reason such as PI, supervisor, or sponsor request. Any IRB member or HRPP professional staff can perform a QA review or site visit, except where any potential conflict of interest exists. The PI will be notified in writing of any findings or opportunities to improve.

10.1.1. A QA review will consist of an examination of records held by the IRB and completion of the associated audit form (see the AFRL IRB web site for the template) to ensure compliance with all administrative requirements as set forth in applicable regulations, policies, and protocol documents.

10.1.2. A QA site visit will consist of a one-on-one interview with the PI, possibly a tour of the research facilities and interviews with staff, and completion of the associated audit form (see the AFRL IRB web site for the template). Observation of the informed consent process or data collection may also be accomplished at the discretion of the IRB representative conducting the visit.

10.2. **Internal.** Internal audits refer to those reviewing IRB and other HRPP administrative activities. These may be random as part of an ongoing QA/Quality Improvement (QI) program; grouped by individual or responsibility level (e.g., administrator, EDO, HRPO, IRB member, etc.), review process or category, risk level, or study parameter; triggered by an incident such as change in risk level, adverse event, allegation (e.g., conflict of interest, misdetermination, misconduct, etc.), or researcher or sponsor complaint; or other reason such as PI, supervisor, or sponsor request. Any IRB member or HRPP professional staff can perform a QA/QI review, except where any potential conflict of interest exists. The HRPP Director (711 HPW/IR) will be notified in writing of any findings or opportunities to improve.

11. Subject Recruiting Policy. Federal guidelines consider direct advertising for study subjects to be the start of the informed-consent and subject-selection process. All recruitment materials or methods (e.g., ads, flyers, e-mails, briefings, telephone recruitment scripts, etc.) must be reviewed and approved by the IRB as part of the package for initial reviews of and amendments to protocols.

11.1. **Subject Recruitment**. Generally, any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. The AFRL IRB, therefore, requires that advertisements be limited to the following information, as recommended in FDA guidance regarding subject recruitment:

11.1.1. The name and address of the investigator and/or research facility;

11.1.2. The condition under study and/or the purpose of the research;

11.1.3. In summary form, the criteria that will be used to determine eligibility for the study;

11.1.4. A brief list of participation benefits, if any;

11.1.5. The time or other commitment required of the subjects; and

11.1.6. The location of the research and the person or office to contact for further information.

11.2. **Responsibilities.**

11.2.1. The PI must have all recruiting documents and ICDs which do not have limited distribution, and hence would be releasable to the public cleared by the Public Affairs (PA) and Scientific & Technical Information (STINFO) review processes IAW 711 HPW OI 61-200, 711 HPW Scientific and Technical Information (STINFO) Security and Policy Review Program Management, AFRLI 61-204 AFRL Scientific and Technical Information (STINFO) Program, and AFI 35-102 Security and Policy Review Process. The PA clearance case number should appear on all recruiting documents and the ICD.

11.2.2. The IRB will review the information contained in the recruitment material and the mode of its communication to determine that the recruiting procedures are appropriate, not coercive. The protocol must contain sufficient detail on the recruiting procedures (e.g., who will do the recruiting, when and how it will be done, etc.) to allow this determination to be made.

11.3. **Preventing Coercion**. Special attention to preventing coercion must be addressed in the protocol when recruiting military subjects. It must be made clear that commanders and supervisors will not be involved in the recruiting process in any way. Personnel in a position of authority must not promote participation or be present during subject recruiting briefings nor will they be made aware of who does and does not volunteer. Refer to DoDI 3216.02_AFI 40-402 for additional details.

11.4. **Reimbursement**. DoDI 3216.02_AFI 40-402 specifies limitations on reimbursements. When reimbursement will be provided to subjects, it can be stated in the advertisement that subjects will be compensated for time, travel, and inconvenience.

12. Conflicts of Interest. A conflict of interest refers to situations in which financial or other personal considerations may adversely affect, or have the appearance of adversely affecting, an individual's professional judgment in exercising any duty or responsibility related to the design and execution of research or other professional activities.

12.1. **Declaration of Potential Conflict(s) of Interest.** All personnel involved in the conduct or oversight of human research have a responsibility to identify and eliminate or mitigate any potential conflict of interest and fully disclose to subjects that such a conflict exists when it cannot be eliminated.

12.1.1. The IRB chairperson will remind members at the beginning of each meeting to declare any conflict of interest and recuse themselves from voting where appropriate.

12.1.2. Investigators will notify the IRB administrative office in writing of a potential conflict of interest on any given protocol.

12.1.3. The ICD shall list all sponsors of the research and any potential conflict of interest that have not been eliminated. General financial relationships do not need to be disclosed; only specific information as it relates to a given research protocol. A financial interest means anything of monetary value and includes but is not limited to the following:

12.1.3.1. Salary or other payments for services (e.g., consulting fees, honoraria, gifts, or employment with an outside organization);

12.1.3.2. Equity interests (e.g., stocks, stock options, or other ownership interests);

12.1.3.3. Intellectual property rights (e.g., patents, copyrights, and royalties from such rights); or

12.1.3.4. Membership on a governing board.

12.1.4. To avoid a conflict of interest, or the perception of such, senior members of organizations (e.g., Department/Division Chiefs and their deputies as well as Branch Chiefs and their deputies) who are also members of the IRB, will abstain from voting when protocols from their departments/divisions or branches are being presented.

12.2. **Appearance of Conflict.** The mere appearance of a conflict may be as serious and potentially damaging as an actual distortion of instructional, research, or administrative goals, processes, or outcomes. Apparent conflicts, therefore, should be disclosed and evaluated with the same vigor as actual conflicts.

13. Protocol Design. Good protocol design is the key to minimizing the risks of human research. The goal of the design and review process is to see that the smallest possible number of subjects is exposed to the lowest possible level of risk and discomfort while still meeting the objectives of the research. The experimental objective must clearly justify the use of human subjects.

13.1. **Risk Reduction.** Techniques include use of existing knowledge, use of alternative methods that do not involve human subjects, statistical design to use the fewest possible subjects, medical screening of subjects if appropriate, monitoring during experiments, and implementation of a safety program.

13.2. **Format.** The most current protocol and ICD templates available on the AFRL IRB web site and instructions are designed to ensure that all of the required information is included in the protocol and ICD. Investigators are urged to follow the established protocol and ICD format template, because they account for all required elements. If a different format is used, the different format must contain all elements required in relevant HRPP regulations and AF instructions.

14. Approval and Oversight Authorities. In addition to the AFRL IRB, there are other levels of research oversight within the Air Force and the DoD.

14.1. **711 HPW and AFRL Relationship**. The AFRL IRB administrative office (711 HPW/IR) is the first level of approval and oversight authority for research conducted or supported by AFRL. All final written approval to investigators to begin research comes from this office.

14.2. **Headquarters Air Force**. AFMSA/SGE-C is the second level and final approval authority for all human research conducted or supported by AFRL. This office does not have an IRB, but performs headquarters review for compliance issues related to IRB determinations. If the protocol requires an Assurance of Compliance, it must be approved before research can begin.

14.2.1. Protocols determined to involve minimal risk may begin once written approval from the IRB administrative office has been issued. The protocol and records of its approval are forwarded to AFMSA/SGE-C for their review and records, but may be subject to modifications or requests for additional information before research can begin.

14.2.2. Protocols determined to involve greater-than-minimal risk, non-lethal weapons, and international research requires approval by AFMSA/SGE-C before research can begin.

14.2.3. When needed, the Surgeon General's Human and Animal Research Panel (SGHARP) will review research deemed controversial or high-risk in addition to the research designated for AFMSA/SGE-C review by DoDI 3216.02_AFI 40-402.

14.3. **Department of Defense**. The Assistant Secretary of Defense for Research and Engineering (ASD(R&E)) [under the authority, direction, and control of the Under Secretary of Defense for Acquisition, Technology, and Logistics (USD(AT&L))] is 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 DoD on matters pertaining to research involving human subjects.

14.3.1. The ASD (R&E) maintains oversight over each of the DoD Components' second-level review authorities, which is AFMSA/SGE-C for the Air Force's HRPP.

14.3.2. The Assistance Secretary of Defense for Health Affairs (ASD(HA)) [under the authority, direction, and control of the Under Secretary of Defense for Personnel and Readiness (USD(P&R)] advises 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.

THOMAS J. MASIELLO, Major General, USAF
Commander

Attachment 1

GLOSSARY OF REFERENCES AND SUPPORTING INFORMATION

References

10 USC 980, Limitations on Use of Humans as Experimental Subjects, 1 October 1985

21 CFR 50, Protection of Human Subjects (FDA), 1 October 2003

21 CFR 56, Institutional Review Boards (FDA), 1 April 2002

32 CFR 219, Protection of Human Subjects (DoD), 1 July 2006

45 CFR 46 (subparts B, C, and D), Protection of Human Subjects (DHHS), 1 October 2003

711 HPW OI 61-1, Research Ethics within the 711th Human Performance Wing, 15 May 2014

711 HPW OI 61-200, 711 HPW Scientific and Technical Information Security and Policy Review Program Management, 27 January 2014

AFI 35-102, Security and Policy Review Process, 20 October 2009 AFI 91-204, Safety Investigations and Reports, 10 April 2014

AFRLI 61-103, AFRL Test Activity Involving Human Participants, 18 June 2014

AFRLI 61-204, AFRL Scientific and Technical Information Program, 29 September 2010

AFPD 40-4, Clinical Investigation and Human Use in Medical Research, 11 May 1994

DoDI 3210.7, Research Integrity and Misconduct, 14 May 2004

DoDI 3216.02_AFI 40-402, Protection of Human Subjects and Adherence to Ethical Standards in Air Force Supported Research, 10 September 2014

Prescribed Forms

None

Adopted Forms

AF Form 847, Recommendation for Change of Publication, 22 September 2009

Abbreviations and Acronyms

AF—Air Force

AFMSA—Air Force Medical Support Agency

AFRIMS— Air Force Records Information System

AFRL— Air Force Research Laboratory

AI—Associate Investigators

AIO—Authorized Institutional Official

ASD—Assistant Secretary of Defense

ATL—Acquisition, Technology, and Logistics

CITI—Collaborative Institutional Training Initiative

CFR—Code of Federal Regulations

DCL—Directorate Cover Letter

DHHS—Department of Health and Human Services

DoD—Department of Defense

EDO—Exempt Determination Official

FDA—Food and Drug Administration

FOUO—For Official Use Only

FWA-Federal-Wide Assurance

HA—Health Affairs

HIPAA—Health Insurance Portability and Accountability Act of 1996

HRPO—Human Research Protection Official

HRPP—Human Research Protection Program

ICD—Informed Consent Document

IO—Institutional Official

IRB—Institutional Review Board

OHRP—Office of Human research Protections

OPR—Office of Primary Responsibility

PI—Principal Investigator

PII—Personally Identifiable Information

PHI—Protected Health Information

P&R—Personnel & Readiness

PRIM&R—Public Responsibility in Medicine and Research

RDS—Records Disposition Schedule

QA—Quality Assurance

QI—Quality Improvement

R&E—Research & Engineering

SG—Surgeon General

SGE-C—Research Oversight and Compliance Division

SGHARP—Surgeon General's Human and Animal Research Panel

STINFO—Science & Technical Information

USD—Under Secretary of Defense

UPIRTSO—Unanticipated Problems Involving Risk to Subjects or Others