BY ORDER OF THE COMMANDER
AIR FORCE RESEARCH LABORATORY
(AFRL)

AIR FORCE RESEARCH LABORATORY
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Medical Command

PROTECTION OF HUMAN SUBJECTS IN RESEARCH

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This instruction describes AFRL procedures for implementing Department of Defense Instruction (DoDI) 3216.02_Department of the Air Force Instruction (DAFI) 40-402, *Protection of Human Subjects and Adherence to Ethical Standards in DAF-Conducted and -Supported Research*, and the Title 32, Code of Federal Regulations (CFR), Part 219, *Protection of Human Subjects*, current edition and defines AFRL's Human Research Protection Program (HRPP). This instruction applies to all AFRL personnel. Ensure all records generated as a result of processes prescribed in this publication adhere to Air Force Instruction (AFI) 33-322, *Records Management and Information Governance Program,* and are disposed in accordance with (IAW) the Air Force Records Disposition Schedule. which is located in the Air Force Records Information Management System. Refer recommended changes and questions about this publication to the office of primary responsibility (OPR) using DAF Form 847, *Recommendation for Change of Publication*, route DAF Forms 847 from the field through the appropriate functional chain of command. This instruction may not be supplemented. Submit requests for waivers through the chain of command to the publication OPR IAW AFRL Delegation of Waiver Approval Authority of Tier Compliance Items Memorandum.

SUMMARY OF CHANGES

This document has undergone a major revision and should be completely reviewed.

1. Applicability.

1.1. This instruction covers all AFRL-conducted or -supported research activities, including tests and evaluation, that involve humans, human data, human biospecimens, or activities regulated by the Food and Drug Administration (FDA). It 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, such as through contracts or collaborative arrangements.

1.1.1. This instruction applies to all Large Scale Genomic Data (LSGD) collected from DoD-affiliated personnel whether or not the activity constitutes human subject's research. For more information on AFRL requirements for genetic research see **Attachment 2**.

1.1.2. DoD/DAF-conducted human research refers to studies where DoD, DAF, or AFRL affiliated personnel are engaged in human research. "Engaged" is defined as interacting or intervening with human subjects or obtains information or biospecimens through intervention or interaction with the individual, or identifiable private information, or biospecimens.

1.1.3. DoD/DAF-supported human research refers to non-DoD support or assistance which may include but is not limited to funding, program management, personnel, equipment, facilities, and access to participant populations.

1.1.4. Tests of materiel includes the development, test, and evaluation of systems and materiel. This instruction is applied when human subjects are involved in a research context. When the activity does not involve human subjects research (HSR), irrespective of risk, this instruction will not apply, and AFRL Instruction (AFRLI) 61-103, Volume 2, *AFRL Test Activity Involving Human Participants*, should be applied.

1.1.5. AFRL personnel are responsible for ensuring any activity or product development involving human subjects or their data or biospecimens is evaluated by the AFRL HRPP office (711th Human Performance Wing, Institutional Review, 711 HPW/IR) to ensure compliance with this instruction and its references, as applicable. Only designated HRPP personnel may make official determinations as to whether such activities include HSR or are exempt HSR per DoDI 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -Supported Research*, **paragraph 3.5**a.(7).

1.2. All human research -conducted or -supported by the AFRL, regardless of source of funding, will be guided by the ethical principles as reflected in Federal Register (FR) Volume 44, Number 76, *Belmont Report: Ethical Principals and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*.

1.3. AFRL will only conduct or support research which is ethical and conducted IAW applicable Federal, DoD, and DAF HRPP requirements.

1.4. This instruction, including separate procedures incorporated by reference to this instruction, serves as the AFRL HRPP Plan. 711 HPW/IR implements the AFRL HRPP, which includes the AFRL Institutional Review Board (IRB), AFRL Human Research Protection Official (HRPO) Program, and FDA regulated activities.

1.5. All persons subject to this AFRL HRPP are responsible to discharge applicable human research protection regulations, AFRL HRPP plan, related institutional policies, and the policies and procedures of the designated IRBs. This includes the Institutional Official (IO), Alternate IO (AIO), the AFRL IRB, HRPOs, Principal Investigators (PIs), and the research community at large.

2. Responsibilities.

2.1. **Department of the Air Force (DAF) Human Research Protection Plan (HRPP) Alignment.**

2.1.1. Office of Under Secretary of Defense for Research and Engineering (USD[R&E]) is the single DoD point of contact for the DoD HRPP. USD(R&E) oversees implementation of the DoD Component HRPPs, to include the DAF HRPP.

2.1.2. DAF Surgeon General (DAF/SG) is the single DAF point of contact for the DAF HRPP and serves as the Senior Designated Official (SDO).

2.1.3. DAF Component Office of Human Research Protections (COHRP) implements the DAF HRPP by authority delegated from AF/SG.

2.2. **AFRL Commander (AFRL/CC), dual-hatted as the Human Research Protection Official** (**HRPP) Institutional Official (IO).**

2.2.1. AFRL Commander (AFRL/CC).

2.2.1.1. Serves as AFRL's IO pursuant to the roles and responsibilities of the IO as applicable to the AFRL HRPP per DoDI 3216.02_DAFI 40-102. Ensures compliance of AFRL's HRPP and ensures human research is conducted with integrity and IAW ethical standards. Has authority and responsibility to enforce HRPP requirements.

2.2.1.2. Establishes AFRLI 40-402 which serves as the AFRL HRPP plan. Will review this HRPP plan to assess whether it provides the desired results in furtherance of compliance per DoDI 3216.02, Part 3.3(a). The IO will approve substantive revisions to this HRPP Plan and will coordinate DAF COHRP approval through the AFRL Human Protections Director (HPD).

2.2.1.3. Establishes an institutional process to identify and monitor HSR activities.

2.2.1.4. Will staff and resource the AFRL HRPP to maintain appropriate expertise, compliance, and effective functioning of the HRPP.

2.2.1.5. May delegate to the 711 HPW/CC and 711 HPW, Deputy Director (DD) the respective duties of this section via AIO roles per DoDI 3216.02_DAFI 40-102.

2.2.1.6. Designates in writing a HPD to oversee the daily operations of the AFRL-conducted and -supported HRPPs as described below. When engaged in HSR, will identify an alternate HPD to perform the HPD duties for the HPD's HSR.

2.2.2. Institutional Official (IO). The following duties may not be further designated.

2.2.2.1. Obtains, maintains, and serves as the signatory official for required assurances of compliance with Federal or DoD requirements for the protection of human subjects. Ensures AFRL submits timely requests for renewal of any required assurance before expiration, upon arrival of a new IO, or for a change in AFRL IRB Chair.

2.2.2.1.1. Maintains a DoD Assurance approved by the DAF COHRP and updates the DoD Assurance with DAF COHRP assistance, as required.

2.2.2.1.2. If AFRL becomes engaged in nonexempt human research supported by Department of Health and Human Services (DHHS), obtains, and maintains a Federalwide Assurance (FWA) from Office of Human Research Protections (OHRP).

2.2.2.1.3. Is responsible for institutional compliance with Federal and DoD regulations and policies (See **Attachment 1**).

2.2.2.1.4. Is available to the HPD, AFRL IRB Chair, and DAF COHRP as needed for issues of concerns not resolved at a lower authority.

2.2.2.1.5. Completes required IO human research training.

2.2.3. Institutional Official (IO). The following duties may be designated to an Alternate IO.

2.2.3.1. Will implement, maintain, and evaluate for improvements this AFRL HRPP Plan, to include evaluation of resources and customers to ensure necessary compliance.

2.2.3.2. Will implement compliance with the FDA and Food, Drug, and Cosmetics (FD&C) Act, on the use of investigational products and test articles to include use of International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) in the use of investigational products.

2.2.3.2.1. Ensures that policies and procedures are developed that comply with FDA, Federal, DoD, and DAF regulations for investigations using FDA-regulated products in humans.

2.2.3.2.2. Directs the 711 HPW, Institutional Research (IR) Regulatory Compliance Office to coordinate, monitor, review, and approve research studies that are conducted or supported by AFRL that involve the use of FDA-regulated products.

2.2.3.2.3. Serves as “sponsor” for all AFRL conducted research involving an FDA-regulated product used under either an Investigational New Drug (IND) or Investigation Device Exemption (IDE) application when no academic or commercial entity is sponsoring the FDA application.

2.2.3.3. Will establish a Post Approval Monitoring Program (PACM) to monitor institutional research to ensure regulatory compliance.

2.2.3.4. May extend the AFRL DoD Assurance to cover human research conducted by researchers without their own DoD or FWA via Individual Investigator Agreements (IIAs).

2.2.3.5. Determines, on behalf of AFRL, considering the local mission, whether to permit research.

2.2.3.6. May suspend or terminate approval of research.

2.2.3.7. Ensures personnel discharging authority of the AFRL HRPP do not disclose or divulge any confidential, proprietary, or private information that is revealed during protocol review and approval, to any third party for any purpose, unless authorized to do so.

2.2.3.8. Facilitates collaborative human research by eliminating or minimizing duplication of efforts by supporting reliance upon a single IRB for any collaborative or multi-site research supported by the Institution, to the extent permitted by law and policy. May enter into agreements, including Institutional Agreement for IRB Reviews (IAIR) to enable this process.

2.2.3.9. Ensures there is no undue influence placed on the review efforts which are overseen by the AFRL HRPP.

2.2.3.10. Provides a local institutional environment that identifies and strives to reduce the possibility for conflict of interest (COI) by personnel responsible for protecting human subjects. Is responsible for ensuring disclosure of actual or potential research-related COIs. The IO/AIO will not serve as an AFRL IRB member to avoid any appearance of institutional COI.

2.2.3.11. Appoints and removes experienced AFRL IRB Chair/Vice Chair, IRB members, and AFRL HRPOs. All such actions are made in writing and remain valid until such time as further action is deemed necessary. Letters of removal will state the reason(s) for removal.

2.3. **Alternate Institutional Official (AIO).**

2.3.1. Discharge of authority reserved to 711 HPW/CC and/or the 711 HPW/DD. When appropriate, others with comparable experience and related qualifications are equally capable of discharging AIO duties and will serve in such capacity upon written delegation by the IO.

2.3.2. Completes required AIO human subjects research training**.**

2.4. **711HPW/IR Director.**

2.4.1. Holds the executive leadership responsibility of 711 HPW/IR.

2.4.2. Supervises the 711 HPW/IR personnel and coordinates efforts across IR.

2.4.3. Delegates responsibility to perform specified duties to personnel under their supervision as required and ensures training is commensurate with duties as delegated. These responsibilities will not be further delegated.

2.5. **711HPW/IR, Deputy Director (DD).** Serves on behalf of the 711 HPW/IR Director.

2.6. **Human Protections Director (HPD).**

2.6.1. Serves as the primary point of contact for the AFRL HRPP and ensures the ethical treatment of human subjects and compliant administration of the AFRL HRPP. The HPD must be sufficiently qualified through experience and expertise.

2.6.2. Reviews the AFRL HRPP plan on an annual basis to ensure it remains current and effective. Prior to initiation, obtains IO/AIO approval of substantive revisions to the AFRL HRPP, and ensures DAF COHRP approval.

2.6.3. Supervises daily operations of the AFRL HRPP to discharge regulated HSR activity as determined by the review authority per DoDI 3216.02_DAFI 40-402, Table 1 to comply with this instruction.

2.6.4. Coordinates resources and establishes processes/standard operating procedures (SOP) for the efficient functioning of the AFRL HRPP in coordination with the AFRL IRB Chair to discharge HSR requirements. Engages in continual process evaluation and improvement of the HRPP.

2.6.5. Facilitates and ensures timely reporting to the DAF COHRP in coordination with the AFRL IRB Chair. These reports will provide sufficient detail and documentation to support understanding and will be provided via email within the required timelines IAW, DoDI 3216.02_DAFI 40-402 or as directed by DAF COHRP. DAF COHRP will coordinate any additional reporting required to higher levels of authority (e.g., USD(R&E)).

2.6.5.1. Mandatory reporting items per DoDI 3216.02_DAFI 40-402 to include a summary of the item(s) and corrective action(s) taken or recommended.

2.6.5.2. Any research that requires Component Level Administrative Review (CLAR) per DoDI 3216.02_DAFI 40-402.

2.6.5.3. Changes to the AFRL HRPP Plan and AFRL HRPP personnel, including IRB member appointments and removals.

2.6.5.4. Provide an Index of HRPP/IRB activity for all DoD-conducted and -supported research on a yearly basis and prior to any compliance assessment. Include with this index all dates of IRB meetings since the last report, full roster of IRB members, and determination of not research/not HSR activity.

2.6.5.5. Any requested items related to the AFRL HRPP, including minutes and samples of HSR review authority determinations made by AFRL HRPP personnel.

2.6.6. Oversees institutional activities and ensures procedures for and monitors all AFRL review authority to comply with DoDI 3216.02_DAFI 40-402.

2.6.7. Ensures the AFRL IO and AFRL IRB Chair remain informed of HRPP updates and requirements. Provides briefings when requested.

2.6.8. Encourages collaboration among and feedback from the HRPP staff to meet mission needs and orchestrates outreach efforts to bring awareness to the institution’s HRPP.

2.6.9. Implements PACM by assigning qualified HRPP personnel to annually monitor HRPP compliance across the enterprise through a representative sample of HSR, including research utilizing FDA-regulated products. Evaluates compliance, procedural effectiveness, and overall efficiency to eliminate operational redundancy of the PACM.

2.7. **AFRL Institutional Review Board (IRB) Chair.**

2.7.1. Serves as the senior AFRL IRB subject matter expert. The AFRL IRB Chair must be sufficiently qualified through experience and expertise, to include serving one year on the AFRL IRB unless waived by the IO.

2.7.2. Completes initial and continuing human research protection training IAW DoDI 3216.02_DAFI 40-402 and Office of the Assistant Secretary of Defense Memorandum, *Minimum Education Requirements for DoD Personnel Involved in Human Research Protection*. This may be symposia, course work, sponsored training by DAF COHRP or recognized national agencies, to include, but not limited to: training conducted by Public Responsibility in Medicine and Research (PRIM&R), and the Collaborative Institutional Training Initiative (CITI) training modules required for IRB members.

2.7.3. Reviews requests for the institution's support for activities that could include human research to ensure compliance with applicable requirements and accepts other institution's assurances as applicable to facilitate collaboration in support of these activities.

2.7.4. Serves as the principal AFRL IRB member responsible for the overall conduct of the AFRL IRB. Leads reviews to ensure compliance with applicable regulations and requirements of this instruction consistent with 32 CFR Part 219 and 44 FR 23192.

2.7.4.1. Ensures the AFRL IRB operates in a timely, professional manner. Provides each AFRL IRB member an opportunity to discuss relevant board activity and coordinate necessary actions to ensure proper board functions.

2.7.4.2. Ensures the AFRL IRB considers scientific merit of proposed research activities, including those utilizing FDA-regulated products.

2.7.4.3. Ensures HSR complies with the DoD ethical principles for Artificial Intelligence (AI) per DoDI 3216.02_DAFI 40-402 when applicable.

2.7.4.4. Ensures medical consultation is provided for protocols with medical related science or risks and for protocols utilizing FDA-regulated products.

2.7.4.5. Reviews and approves AFRL IRB minutes ensuring IRB actions and determinations are documented and accurate.

2.7.5. Provides required regulatory review of activities submitted through the AFRL IRB office. Will discern which projects are research, those which involve human subjects, or are otherwise deemed exempt per the Common Rule (32 CFR Part 219). Completes expedited IRB reviews and signs the IRB's outcome letters. Holds authority to designate, in writing, expedited IRB duties to any other duly appointed AFRL IRB members.

2.7.6. Consults with other subject matter experts (SME) and committees as needed to support the ethical, safe, and regulatory compliant review of proposed research.

2.7.7. Declares personal COIs and will immediately secure self-recusal during any period of affected deliberation, voting, or other required board action.

2.7.8. Recommends to the IO/AIO qualified individuals for AFRL IRB membership and provides members with written appointments.

2.7.9. As first recommended by the AFRL IRB Chair, a Vice Chair shall be appointed by the IO/AIO in writing. Any candidate selected as Vice Chair will, at a minimum, be an IRB member who is sufficiently familiar with the day-to-day operations of the AFRL IRB office. Upon formal appointment, the Vice Chair shall have authority to act on behalf of the AFRL IRB Chair whenever the latter is unavailable to discharge required duties.

2.8. **Intramural Lead (AFRL-Conducted Research).**

2.8.1. Is responsible for maintaining the AFRL-conducted human research program, including the AFRL IRB. The Intramural Lead serves as the Deputy HPD for intramural matters and must be sufficiently qualified through experience and expertise.

2.8.2. Coordinates and leads reoccurring HSR training for AFRL personnel.

2.8.3. Maintains FWA when required and IRB registration with OHRP, and updates as required.

2.8.4. Maintains the DoD Assurance issued by DAF COHRP and is the POC for compliance assessments, FDA, and other inspections.

2.8.5. Oversees the daily operations of AFRL-conducted research activity and coordinates work across the IRB administrators/analysts.

2.8.6. Ensure timely reviews of protocols and take steps to reduce administrative burden and minimize delays.

2.8.7. Keeps the HPD and AFRL IRB Chair informed of the status and any issues with AFRL-conducted research.

2.8.8. Completes human research protections training and maintains an expert level of competency related to human subjects regulations and ethical standards.

2.9. **Extramural Lead (AFRL-Supported Research).**

2.9.1. Responsible for maintaining the AFRL-supported human research program. The Extramural Lead serves as the Deputy HPD for extramural/HRPO matters and must be sufficiently qualified through experience and expertise.

2.9.2. Coordinates and Leads reoccurring HRPO training.

2.9.3. Oversees the daily operations of AFRL-supported research activity and coordinates work across the HRPOs.

2.9.4. Ensure timely reviews of HRPO submissions and take steps to reduce administrative burden and minimize delays.

2.9.5. Completes human research protections training and maintains an expert level of competency related to human subjects regulations and ethical standards.

2.10. **Institutional Review Board (IRB) Administrator/Analyst.**

2.10.1. Responsible for the day-to-day administrative operation of the AFRL IRB office. The administrator/analyst should be an expert on HRPP matters, able to assist investigators, the IRB, and all levels of leadership in matters which routinely come before an IRB.

2.10.2. Completes initial and continuing human research protection training.

2.10.3. Maintains expertise in and implements the requirements of 32 CFR Part 219 and DoDI 3216.02_DAFI 40-402, this instruction, and other requirements applicable to human research.

2.10.4. Actively tracks the status of activities submitted to and overseen by the IRB, including human research protocols that are labelled not research, not human subjects research, exempt and nonexempt; pending approval; active and ongoing; or matters which are either closed or recommended for closure.

2.10.5. Maintains required documentation and records for all activities submitted.

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

2.10.7. Maintains communications with each PI regarding human research protection issues. In addition, will inform PIs of the requirements to submit progress reports and a "final report".

2.10.8. Performs a substantive administrative review of all protocol submissions and ensures that all submission requirements are received before processing for review and approval.

2.10.9. Prepares and manages monthly IRB meetings.

2.11. **AFRL Institutional Review Board (IRB) Member.**

2.11.1. Service as an AFRL IRB member is a highly valued, voluntary, privileged, additional duty.

2.11.2. Completes HRPP training per the DoDI 3216.02_DAFI 40-402 and USD(R&D).

2.11.3. Regularly attends and actively participates in monthly AFRL IRB meetings. Reads all relevant materials prior to each convened meeting and will be prepared to participate in all issues which come before the IRB pursuant to 32 CFR Part 219.107.

2.11.4. Preemptively declares any COIs and timely recuses themselves from voting, whenever factual conditions so require.

2.11.5. Notifies the AFRL IRB Chair of their intent to leave the IRB with as much advanced notice as possible and will include the reason for leaving said role.

2.12. **Exempt Determination Official (EDO).** AFRL does not utilize EDOs and instead utilizes designated AFRL IRB members to conduct evaluations and determinations for not research, not human subject research, and exempt determinations per 32 CFR Part 219.

2.13. **Human Research Protection Official (HRPO).**

2.13.1. The purpose of the HRPO is to ensure compliance of non-DoD conducted, DoD-supported human research. The HRPO will ensure DoD and DAF requirements are satisfied. AFRL HRPOs exercise written delegation of authority from DAF COHRP, with visible, coordinated appointment of same by and through the IO/AIO chain of command.

2.13.2. AFRL HRPO. HRPO is a federal employee who is appointed by the AFRL IO or an AIO and located within 711 HPW/IR. In selecting an AFRL HRPO, the IO/AIO will consider potential candidate's qualifications and potential COIs (both actual and perceived).

2.13.3. The AFRL HRPO reviews DoD Supported HSR conducted by a non-DoD institution which includes or are likely to include HSR (as indicated by their agreement with DoD [e.g., contract, grant, cooperative research and development agreements, or other agreement]) to ensure compliance with this issuance. When more than one DoD institution provides support, the HRPO of the institution executing a contract or similar award to the non-DoD institution is the HRPO of record (unless deferred to an equivalent HSR review authority IAW DoDI 3216.02_DAFI 40-402). The AFRL HRPO will rely on other DoD HRPO review authorities to avoid duplication of effort.

2.13.4. The AFRL HRPO will not be required to maintain approvals or ongoing documentation of protocols that are under the purview and oversight of an alternate DoD components' HRPO.

2.13.5. The AFRL HRPO must concur with the non-DoD HRPP's determination of activity that are either determined by the non-DoD HRPP to be not research, research not involving human subjects, exempt research (including those under a limited IRB review) or nonexempt HSR prior to the start of the activity.

2.13.6. Coordinates with the Program Manager (PM) or Program Officer throughout the lifespan of the approved protocol to ensure compliance with all DoD requirements governing HSR.

2.13.7. Coordinates with DoD PM /officers and the non-DoD performer to receive complete submission packages in order to initiate HRPO review and works with the performer to resolve missing information or incomplete documentation to allow for final HRPO concurrence.

2.14. **FDA-regulated Activities Consultant and Compliance Officer (FRACCO).**

2.14.1. Serves in a primary consulting role for investigators, the 711 HPW/IR Director, and IO/AIO when FDA-regulated investigational products are being used in HSR.

2.14.2. Maintains personnel expertise and other resources to advise on research activities involving FDA-regulated investigational products.

2.14.3. Serves as the primary point of contact to advise on formal and informal communications with the FDA for research involving FDA-regulated investigational products.

2.14.4. Ensures that all the sponsor's responsibilities for FDA-regulated investigational products are fulfilled IAW Title 21 CFR Part 312, *Investigational New Drug Application,* current edition Subpart D and Title 21 CFR Part 812, *Investigational Device Exemptions*, current edition Subpart C and G and executed through written delegation when internal to AFRL or through signed agreements with external collaborators.

2.14.5. Ensures AFRL-sponsored IND and Investigation Device Exemption (IDE) applications, amendments, New Drug Applications (NDA), Biologics Licensing Applications (BLA), IDEs, 510(k), and Premarket Approval Applications (PMA) are complete and accurately submitted to the FDA.

2.14.6. Conducts post-marketing surveillance for AFRL-sponsored NDAs, BLAs, IDEs, 510(k), and PMAs IAW Title 21 CFR Part 314, *Applications for FDA Approval to Market a New Drug*, current edition Title 21 CFR Part 601, *Licensing*, current edition and Title 21 CFR Part 814, *Premarket Approval of Medical Devices*, current edition.

2.14.7. Ensures that appropriate safety monitoring of AFRL-sponsored research involving FDA-regulated investigational products is conducted in accordance with FDA regulations and guidance using 21 CFR Part 312.32 for definitions and review of safety information/reports, and 21 CFR Part 812.150 regarding unanticipated adverse event(s) associated with the use of FDA-regulated investigational products.

2.14.8. Monitors and ensures that training is available to investigators, so that they may be considered for positions and meet the training and experience criteria required by the FDA.

2.15. **AFRL Program Managers (PM)/Program Officers.**

2.15.1. Must comply with requirements contained in DoDI 3216.02_DAFI 40-402, paragraph 3.6.b when managing activities that include research involving human subjects.

2.15.2. Will coordinate with the non-DoD performer, DoD award officer and AFRL HRPO to facilitate the initial HRPO review and continued oversight of the approved award until completion.

2.15.3. Will incorporate in the management plan adequate lead time for accomplishment of FDA applications, and FDA-related reviews and approvals when an experimental or investigational FDA-regulated product is part of their research portfolio and ensure uninterrupted continuity of the PI and sponsor roles is maintained.

2.15.4. Will be the main POC for the performer for all technical questions and concerns throughout the length of the award.

2.15.5. Will inform the non-DoD performer of their non-delegable responsibility to oversee the timely execution of DoD-supported research and will track the investigators performance and HRPO requirements per the contractual agreement.

2.15.6. Will ensure all solicitations and Broad Agency Announcements (BAA) for DoD-supported research that includes or may include human subjects informs the performer of the following requirements to avoid delays in the HRPO approval process:

2.15.6.1. That the Institution engaged in nonexempt human subjects research must have a current DHHS, OHRP FWA or DoD Assurance.

2.15.6.2. That the DoD supported HSR receives review by a non-DoD IRB and be issued a determination per the Title 45 CFR Part 46, *Protection of Human Subjects*, current edition (Subparts B, C, and D) (by one of the IRBs listed on the institution's assurance) or identified in an Institutional Agreement for IRB Review.

2.15.6.3. Will notify the AFRL HRPO immediately of any change in program oversight or in the event of the replacement of the PM or Program Officer for HSR under AFRL HRPO oversight.

2.16. **Procurement, Contracts, and Grants Officers.**

2.16.1. Ensures FAR-based contracts (and comparable language for other transactional agreements) for DoD-supported research involving human subjects, includes the Defense Federal Acquisition Regulation Supplement (DFARS) Clause, 252.235-7004, *Protection of Human Subjects*, or comparable language. Such language instructs awardees to specific requirements and responsibilities during all periods of performance and alerts performers that any research which involves human subjects is to be reviewed and concurred with by a HRPO.

2.16.2. Ensures that DoD contracted performer is aware via the executed award that any research with human subjects may not commence without first undergoing HRPO review and receiving written HRPO concurrence.

2.16.3. Ensures that the Statement of Work includes language from the DoD R&D General Terms and Conditions or comparable language that: award recipients (to include sub-recipients) must not commence DoD-supported HSR, as defined in DoDI 3216.02, to include research with human data and biological specimens, until a DoD HRPO issues formal approval.

2.16.4. Ensures that the prime awardee is informed via the executed award or agreement that the required DFARS clause or comparable language must also flow to any sub awardee.

2.17. **Branch/Division Chief.**

2.17.1. The chief of each AFRL branch/division (or their designee at the department/division level or higher) that conducts or supports research with human subjects, will support the AFRL HRPP by ensuring compliance of division personnel with this instruction and applicable requirements.

2.17.2. Reviews all proposed branch/division HSR protocols and FDA-regulated research activity prior to submission to the IRB. Upon completion of such review, the following matters will have been fully considered and deemed appropriate for IRB consideration:

2.17.2.1. Competence of the principal and associate investigators to carry out the research.

2.17.2.2. Scientific merit of the project as determined by SME, such expertise includes qualified appropriate medical personnel to assess risks and medical related impacts to science. Scientific review is applicable to all exempt and nonexempt research.

2.17.2.3. Relevance of the research to DAF needs.

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

2.17.2.5. Validity of the experimental design must satisfy the following:

2.17.2.5.1. Articulation of a clear and testable hypothesis.

2.17.2.5.2. Establishment of appropriate data quality/security control.

2.17.2.5.3. Adequacy of planned statistical or other analysis appropriate for study type.

2.17.2.5.4. Appropriateness of number of subjects, sufficient for validity.

2.17.2.5.5. Minimization of discomfort and risk to subjects.

2.17.2.5.6. Adequacy of branch/division safety preparedness for medical emergencies, including provision for notification of emergency medical personnel, and first-aid training/capability where applicable.

2.17.2.5.7. Availability of an adequate number of required personnel and resources to conduct the approved protocol and a plan to properly transfer responsibilities when an occasion arises making a program manager/researcher no longer able to perform their role due to Permanent Change of Station (PCS), deployment, change of work organization, retirement, separation or another instance.

2.17.2.5.8. AFRL researchers and developers using FDA-regulated investigational products in humans comply with FDA regulations and recommendations and engage in consultation with the FRACCO.

2.17.3. Establishes branch/division procedures concerning paragraphs **2.17.1 and 2.17.2**. Branches/Divisions will use the AFRL IRB-supplied directorate acknowledgement letter template to document routing of submissions to the IRB.

2.17.3.1. By forwarding of the submission e-mail, signing the directorate acknowledgement letter, the Branch/Division Chief certifies compliance with all items addressed in paragraphs **2.17.1 and 2.17.2**. AFRL HRPP personnel will confirm compliance with relevant requirements for protocol submissions.

2.17.3.2. For FDA-regulated research, the signature attests to approval of the commercial or other sponsor identified in the protocol and the research is conducted in compliance with FDA regulations and this instruction.

2.17.3.3. If the branch/division lacks expertise to deal with a specific research topic or proposed design, the affected office will so note on the directorate acknowledgement letter and will seek appropriate expertise by which to supplement the required review determination.

2.17.4. Immediately notifies the 711 HPW/IR Director of any inquiry of research misconduct or noncompliance, per **paragraph 12**, which involves an investigator, or a member of their team, engaged in human research.

2.17.5. Ensures a program POC is assigned to oversee DoD-supported HSR conducted by a non-DoD institution. That POC shall be the main point of contact with the HRPO throughout all phases of HRPO review. Whenever the POC leaves their assignment, ensures a proper hand-off is accomplished and the AFRL HRPO is notified of their replacement. This POC will complete HSR training as determined by the HRPO.

2.17.6. Provides procedures for storage of research records IAW DoDI 3216.02_DAFI 40-402, and DAF Records Management requirements.

2.17.7. Ensure collaborations with outside institutions comply with the terms set forth in contracts, agreements, and memorandums, including collaborations with commercial sponsors related to FDA-regulated products.

2.18. **Principal Investigator (PI) in Department of Defense (DoD)-Conducted Research.**

2.18.1. A government employee (Active Duty or Civil Servant) with experience and expertise in the scientific field in which they plan to conduct research. There will only be one PI on a protocol.

2.18.2. Understand and ensure their research with human subjects complies with FDA, Federal, DoD, and DAF regulations, this instruction, and any other requirement applicable to HSR. Ensures a determination or approval is received prior to initiating human research activity.

2.18.3. Takes sole responsibility for the supervision and conduct of their research activity, and if deploys or departs from AFRL will secure a replacement PI for all open studies, prior to departure.

2.18.4. Ensures execution of research involving human subjects aligns with terms set forth by the HSR review authority (Determination Official, IRB approval, or DAF COHRP approval).

2.18.4.1. Unless necessary to eliminate immediate hazards to subjects, secures IRB approval prior to implementing changes to approved research activity by submitting an amendment.

2.18.4.2. Submits required continuing reviews (re-approval) and closures of research prior to specified expiration dates and includes a listing of scientific publications and presentations relating to the research.

2.18.5. Obtains written approval from command/component leadership prior to involving DoD-affiliated personnel as subjects in HSR or when conducting research on a DoD facility. Templates for approval are available from the AFRL HRPP.

2.18.6. Promptly (within 5 days) notifies the AFRL IRB office of:

2.18.6.1. Any COIs related to the conduct of research.

2.18.6.2. New information from any source that alters the risks or benefits represented in the protocol.

2.18.6.3. Any adverse events or other unanticipated problem involving risk to subjects or others (UPIRTSO) per **paragraph 11**.

2.18.6.4. Any other information which might affect the subject's decision to participate, or

2.18.6.5. Any allegation of misconduct per **paragraph 11** from any source.

2.18.7. Notifies all interested parties (e.g., Associate Investigators, PMs, Contracting Officers, CoC, etc.) of any IRB disapproval, suspension, or termination of a protocol.

2.18.8. Unless the IRB approves an alternate process, provides each subject with a copy of their informed consent document (ICD).

2.18.9. Will provide adequate storage for all study-related documents for a minimum of three years post study closure or longer if required by the protocol. The responsibility to store study documents resides with the division, even if the original PI is no longer at AFRL.

2.18.10. Will promptly and thoroughly address requirements issued by HSR review authorities in accordance with the HRPP and understands that failure to comply with responsibilities or requirements may lead to suspension of IRB approval for protocol(s), and other corrective actions.

2.18.11. For FDA-regulated research, investigators will comply with requirements in 21 CFR Part 312, Title 21 CFR Part 50, *Protection of Human Subjects*, current edition Title 21 CFR Part 54, *Financial Disclosure by Clinical Investigators*, current edition and 21 CFR 812.

2.18.11.1. Investigator's responsibilities under 21 CFR Part 312, Subpart D are restated in "Commitments" on FDA Form 1572, *Statement of Investigator*, and on the FDA Form, *IDE Application* submitted by the sponsor in 21 CFR Part 812.43(c)(4). The investigator makes an attestation to abide by these responsibilities upon signing and agrees to the following.

2.18.11.1.1. Agree to personally conduct the study in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

2.18.11.1.2. Agree to inform any subjects, or any persons used as controls, that the products are being used for investigational purposes, and will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50, and IRB review and approval in Title 21 CFR Part 56, *Institutional Review Boards*, current edition are met.

2.18.11.1.3. Agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR Part 312.64.

2.18.11.1.4. Agree to read and understand the information in the Investigator's Brochure, including the potential risks and side effects of any drug.

2.18.11.1.5. Agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

2.18.11.1.6. Agree to maintain adequate and accurate records and to make records available for inspection in accordance with appropriate FDA regulations.

2.18.11.1.7. Agree to ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

2.18.11.1.8. Agree to promptly report to the IRB all changes in the research activity and any unanticipated problem involving risks to human subjects or others. Additionally, will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

2.19. **Gatekeepers of Human Subject Research (HSR).**

2.19.1. The IO/AIO, with consultation from the AFRL IRB Chair, will identify personnel within the institution who may see HSR as part of their duties.

2.19.2. These individuals will complete Gatekeeper HSR training provided by the AFRL HRPP to assist the 711 HPW in identifying potential HSR and provide the parties conducting the research with the information to contact the AFRL HRPP/IRB.

3. AFRL-Conducted Human Research.

3.1. This section applies to both AFRL personnel who conduct human research and others covered by the AFRL DoD Assurance through agreements, such as AFRL support contractors or interns (collectively referenced as "AFRL investigators" in this section). It applies to all AFRL investigator activities while on duty for the AFRL.

3.1.1. This section applies regardless of if another HRPP office or IRB is the IRB of record and has primary responsibility for oversight of an activity.

3.1.2. DoD and non-DoD institutions must comply with all the requirements in this issuance when the AFRL HRPP/IRB is the IRB of record.

3.1.3. Research conducted in foreign countries must comply with DoDI 3216.02_DAFI 40-402, and IAW the host nation's applicable laws.

3.1.4. AFRL prohibits the testing of chemical and biological agents except as stated in DoDI 3216.02.

3.2. **General Procedure.**

3.2.1. AFRL investigators will submit to the AFRL IRB office all requests to determine whether proposed activities meet the definition of research involving human subjects. All such requests will meet IRB submission requirements. Specific requirements for DoD-conducted (intramural) research can be found at **https://usaf.dps.mil/teams/10213/default.aspx**, and questions may be directed to **AFRL.IR.ProtocolManagement@us.af.mil**.

3.2.2. The IO/AIO may rely on an HRPP office outside of AFRL, if appropriate, in all such instances, the AFRL IRB office will coordinate.

3.2.3. DAF reliance on a non-DoD IRB requires DoD HRPP deferral to the non-DoD IRB and administrative review conducted by the AFRL IRB Chair (or Chair designee), HRPO, or DAF COHRP prior to initiation of the research. The AFRL IRB office will rely on other DoD and non-DoD institutions HSR review/approval to avoid duplicative reviews and will ensure the following conditions are met:

3.2.3.1. The non-DoD institution has an appropriate FWA when required.

3.2.3.2. The non-DoD IRB is registered IAW 45 CFR Part 46, Subpart E, *Registration of Institutional Review Boards*.

3.2.3.3. All applicable local and DoD requirements are addressed in the protocol.

3.2.3.4. The DoD institution and the non-DoD institution enter into an Institutional Agreement for IRB Reviews (IAIRs) specifying that the non-DoD IRB will apply the DoD requirements specified in this issuance. These agreements are forwarded to the DAF COHRP to update the AFRL DoD Assurance. If the research constitutes classified HSR, the DAF COHRP, on behalf of the SDO, approves the agreement to rely on the non-DoD institution's IRB.

3.2.4. IAIRs and similar agreements should have provisions for post approval monitoring of research activities.

3.2.5. When the IO/AIO rely on another HRPP office, investigators must remain in compliance with the reviewing institution's policies and procedures as well as the applicable requirements of this instruction and its references (See **Attachment 1**).

4. AFRL Institutional Review Board (IRB).

4.1. Implements and complies with all applicable FDA, Federal, DoD, and DAF requirements. Additional AFRL IRB guidance documents, training, and informational sheets provide detail regarding IRB operations and facilitation of regulated requirements within the institution.

4.1.1. The AFRL IRB is permitted to review human research from other institutions at the discretion of the AIO, HPD and the IRB Chair. Such non-AFRL review work will be assessed for resource needs and the AFRL IO will supply the resources as needed. When AFRL provides services to other DoD components, the terms applicable to those services will be explicitly established through agreements.

4.1.2. The AFRL IRB ensures that human research under its review authority is accomplished in an ethical manner; protects the privacy and safety of volunteer participants to the maximum extent feasible IAW the references (See **Attachment 1**) and fulfills legitimate DAF requirements that cannot be reasonably met through non-human testing methodologies. The IRB will make timely, ethical judgments with appropriate levels of scientific merit during all stages of research activity.

4.1.2.1. The AFRL IRB applies the additional protections for vulnerable populations as specified in 45 CFR Part 46, Subparts B, C, and D.

4.1.2.2. The AFRL IRB also applies the additional protections for DoD-affiliated personnel as specified in DoDI 3216.02.

4.2. IRB membership shall be reviewed at least annually by the Chair and adjusted as appropriate. There are no IRB member term limits, and the IO/AIO can dismiss IRB members at any time for any reason.

4.3. **AFRL Institutional Review Board (IRB) Review.**

4.3.1. Consultants. The AFRL IRB may call upon outside consultants as necessary for additional expertise on any matter which requires supplemental perspective, including research activity utilizing FDA-regulated products. Outside consultants are non-voting members who assist the IRB in discharging its core function. As part of the HRPP process, consultants are bound to the terms of confidentiality as described in **paragraph 16**.

4.3.2. Legal Review. A sufficiently trained DAF legal officer will serve as a permanent consultant to the AFRL IRB.

4.3.3. Ancillary Review. Ancillary review of protocols may be required dependent on the type of research activity involved. This includes but is not limited to Public Affairs (PA), Information Technology (IT), Safety, Biosafety, Laser Safety, Radiation Safety, Medical, and Data Analytics.

4.3.4. Requests for IRB Review. AFRL investigators will submit to the AFRL IRB office all items required for review. A submission will not be considered complete until the IRB has received all the required items.

4.3.5. Investigators will be given the opportunity to address the board at the IRB meeting in which their protocol is reviewed, however, they will be excused prior to final board discussions and votes.

4.3.6. Intake Review. The IRB administrator/analyst will review the submission for completion and regulatory criteria. They will provide submissions to the AFRL IRB Chair (or IRB Chair designee) or convened IRB for review.

4.3.6.1. Initial Submissions. The AFRL IRB Chair/designee will determine whether the activity is research and involves human subjects. Any matter, even those which qualify for expedited review, may be considered for review by the full board.

4.3.6.2. FDA Submissions. The AFRL IRB Chair/designee will coordinate with the investigator and FLACCO for review of FDA-regulated activities ensuring scientific and ethical review prior to submission to the FDA.

4.3.6.2.1. The AFRL IRB will be comprised and function in accordance with 21 CFR Part 50, 21 CFR Part 56, and 32 CFR Part 219.

4.3.6.2.2. The AFRL IRB will share protocols and other relevant documents with the FDA for consultation as necessary regarding FDA-regulated products prior to IRB approval.

4.3.6.3. Amendments, Continuing Review Reports, Other Reports. The AFRL IRB Chair/designee will consider whether the item qualifies for expedited review.

4.3.7. Determinations. Qualified AFRL HRPP staff or AFRL IRB members suggested by the AFRL IRB Chair and designated in writing by the AIO may provide determinations on research activities which are not considered research, research not involving human subjects, or research that meets criteria for exempt review per regulatory requirements.

4.3.7.1. Not Research/Not Human Subjects Research (NR/NHSR). NR/NHSR does not meet the regulatory definition of research as specified in 32 CFR 219. AFRL NR/NHSR determinations are made by the AFRL IRB Chair (or IRB Chair designee). This determination must be made before the activity begins; retroactive approval cannot be granted. If a request for NR/NHSR is denied, the PI may pursue exempt, expedited, or full IRB review.

4.3.7.2. Exempt Research. Certain types of human research are exempt from certain regulatory requirements IAW 32 CFR Part 219.104. AFRL exempt determinations are made by the AFRL IRB Chair (or IRB chair designee). This determination must be made before the activity begins; retroactive approval cannot be granted. If a request for exemption is denied, the PI may pursue expedited or full IRB review.

4.3.8. Expedited Review. Nonexempt research involving human subjects that meets criteria set forth in 32 CFR 219.110 may qualify for expedited IRB review procedures. The AFRL IRB Chair (or IRB chair designee) will conduct the expedited review. The reviewer may exercise all IRB authorities except for disapproval. When unable to approve research, the reviewer will refer the research to the convened IRB.

4.3.9. Convened IRB Review. Human research that does not qualify for exemption or expedited review status must be reviewed by the convened IRB.

4.3.9.1. Schedule. The AFRL IRB will convene at least once per month for review of human research. When appropriate, ad hoc IRB meetings may be convened at the discretion of the AFRL IRB Chair to address urgent issue(s). Timely submission equates to three weeks prior to a scheduled IRB meeting date. Adherence to submission deadlines will be strictly observed.

4.3.9.2. Agenda. The AFRL IRB Chair may bring any issue or protocol to the attention of the convened IRB. When appropriate, the Chair may also request a vote on any matter which falls under the decision-making function of the convened IRB.

4.3.9.3. Voting. The IRB may vote as follows: approve, require changes to obtain approval, table for another meeting, or disapprove any aspect of the reviewed protocol.

4.3.9.4. Quorum. A majority of the IRB members must be present, including at least one member whose primary concerns are in nonscientific areas to meet quorum and vote. If the total IRB membership is an even number, then the majority is half plus one. When the IRB membership is an odd number, the majority is calculated by half and rounding up to the next whole number. A quorum must be maintained throughout the meeting. If quorum is lost during a meeting, the IRB may not vote on proposed research.

4.3.9.4.1. Any matter which requires board action shall be deemed approved upon a simple majority vote.

4.3.9.4.2. Abstentions. Although all members free from COIs on a pending motion can, and are able to cast a vote, they cannot be compelled to do so. Any member may choose to abstain if the member feels uncomfortable voting for or against a motion. Members who abstain will provide a reason for the abstention. Abstentions count towards quorum.

4.3.9.4.3. Recusals. Any IRB member with a COI is recused from voting. When a member is recused, that person does not count in the tally of voting members present to satisfy the required quorum count. If member recusal reduces the number of members below quorum, the convened IRB may still discuss the protocol, however, the IRB may not vote on a final action(s) and the affected protocol(s) will be tabled for consideration at the next regularly scheduled IRB meeting.

4.3.10. Release of IRB Determinations or Approvals. All IRB determinations/approvals are documented in writing and will be released to investigators by the AFRL IRB office. The letter will cite regulatory determinations, state the justification, and whether any additional human research protection review and approval is required before the research can begin. If higher level CLAR review is required IAW DoDI 3216.02_DAFI 40-402, the approval letter will not be released to the PI until the CLAR is complete. Initiation of the research to engage with subjects must not begin until the determination/approval letter is provided to the PI.

4.3.10.1. Approval will include a statement that requires the investigator to obtain further IRB approval before implementing changes, to submit continuing review reports, and to report other events, as required. The IRB approval will also include the date of IRB approval, the IRB approval expiration date, and the continuing review due date.

4.3.10.2. IRB approvals are conveyed to the IO/AIO as required by the AFRL IRB office.

4.3.10.3. If proposed research is disapproved either by the IRB or IO/AIO, the PI will be notified, in writing, with an explanation of such disapproval.

4.3.10.4. Approval Dates. Convened board approval dates are the day of the convened meeting when the protocol is approved as written. For convened board protocols which require modifications prior to approval, the approval date will be either the next meeting when the modifications are approved by the IRB or the date the modifications are confirmed by the AFRL IRB Chair or designee. For expedited reviews, the approval date is the day the AFRL IRB Chair or designated reviewer signs the approval documents.

4.3.11. Continuing Review (Re-approval). Convened IRB approvals shall be valid for no less than a period of one (1) year. Expedited protocols will be approved for a period up to five years at the discretion of the IRB reviewer. The rationale for this continuing review period is to provide any new information that should be considered and provided to subjects enrolled in the study, to ensure the safety of participant data to account for investigator turn over, and other similar circumstances. Although the AFRL IRB office will send courtesy notifications of impending review and/or expiration periods for specified protocols, it is the PI's responsibility to ensure all required documentation for re-approval or closure is submitted by the due date as indicated on the most recent IRB approval letter.

4.3.12. Expiration. If IRB approval of continuing review is not completed within the term of approval, IRB approval will expire. In this event, the AFRL IRB office will issue a letter notifying the PI that all human research activities be halted, unless it presents risks to the participants' safety, including analysis of study data, until the research can be reviewed and re-approved. Failure to make a timely renewal is considered noncompliance. The PI, Branch Chief, and Division Chief will submit root cause analysis and corrective actions to avoid a repeat of protocol expiration.

4.3.13. Amendments. Investigators must submit to the AFRL IRB office written requests for IRB approval of any amendment(s) to previously approved HSR and for exempt determinations. Investigators will not implement a proposed amendment to an approved research design or document before it is evaluated and approved by the IRB. The only exception to this requirement is the rare instance when changes are necessary to eliminate/avoid an immediate hazard(s) to human subjects, in which case the change will be considered a protocol deviation that must be promptly (within 5 days) reported IAW this instruction. Amendment requests must detail the proposed changes, the reason for the changes, and a justification for why the changes do not change the risks or benefits of the research.

4.3.13.1. Minor Amendments represent a simple change to a research protocol which does not change the overall risk to subjects. Minor amendments do not alter the research objectives and request nominal changes to enrollment targets, tests performed, and analysis. It does not require additional scientific review, directorate routing, or further ancillary review unless determined by an AFRL IRB Chair/Vice Chair or designee.

4.3.13.2. Major Amendments do not meet the criteria for a minor amendment and requires a new scientific review, new directorate routing, and further ancillary reviews as determined by the AFRL IRB Chair/Vice Chair or designee.

4.3.13.3. Changes to research objectives usually require a new protocol submission rather than an amendment to the currently approved protocol. The PI must justify why research objective changes should be considered as an amendment versus a new protocol. The AFRL IRB Chair/Vice Chair will make the final decision.

4.3.14. Protocol Closure. Each investigator will, upon completion of nonexempt research, submit to the IRB a final status report. The completion report is a formal requirement which acknowledges official closure of a previously approved HSR project. Research is considered complete when the study is closed to subject enrollment and all collection and related analysis of PII, and associated data are complete and the PII disposed of as specified in the protocol.

4.3.15. Suspension or Termination of IRB Approval. The IRB may suspend or terminate previously approved research for concerns regarding subject safety or welfare, or potentially serious or continuous noncompliance. The HPD or AFRL IRB Chair can suspend IRB approval of pending review by the convened IRB. Only the full, convened IRB, however, can terminate IRB approval. If terminated/suspended, the IRB will notify the investigator, Department/Division Chief, IO/AIO, and DAF COHRP of all such decisions. The notification will be provided in writing and include sufficient rationale to support such action. AFRL command authority is independent of the IRB; the IO/AIO may suspend or terminate AFRL human research at any time and for any reason. Neither the IRB or any DAF command authority can override the other’s suspension nor termination.

4.3.16. Appeal of IRB decisions. Investigators have the right to appeal IRB decisions.

4.3.16.1. The investigator will submit the request, in writing, within 30 days of written notification of the IRB’s decision.

4.3.16.2. The convened IRB will review the appeal at which time the investigator will be invited to speak. Upon full assessment of additional matters brought before the board, the IRB will reconsider its decision. The following actions are available: (a) allow the previous decision to stand or (b) reverse all or part of the previous decision.

4.3.16.3. The appeal decision of the IRB will be forwarded to the IO/AIO.

4.3.17. IRB Records. The IRB administrator will maintain case files for each protocol or exempt request submitted to the AFRL IRB office IAW **paragraph 16.2**.

5. AFRL-Supported Human Research. All AFRL supported HSR activities which receive HSR determinations or IRB approvals from a non-DoD institution require AFRL HRPO review. When the AFRL IRB is the IRB of record, the HRPO review is performed in conjunction with the AFRL IRB review. Oversight of the AFRL HRPO program and substantive matters which affect external performers will be approved by the 711 HPW/IR Director in conjunction with DAF COHRP approval prior to initiation IAW DoDI3216.02_DAFI40-402.

5.1. AFRL HRPO general instructions, checklists, information sheets, to include PACM related collection documents, are maintained separately. Specific requirements for DoD-supported (extramural) research can be found at **https://usaf.dps.mil/teams/10213/default.aspx**, and questions may be directed to **AFRL.IR.HRPO@us.af.mil**.

5.2. After a protocol is successfully approved by a non-DoD IRB, the AFRL HRPO will review and either concur or non-concur with the non-DoD IRB's determination. The HRPO will provide justification for a nonconcurrence.

6. Food and Drug Administration (FDA)-Regulated Research. The FDA has statutory authority to regulate scientific studies which are designed to develop evidence to support the safety and effectiveness of investigational drugs, biologic products, cosmetics, and medical devices and regulates the development of these products IAW Title 21 CFR Part 58, *Good Laboratory Practices for Nonclinical Laboratory Studies*, current edition Title 21 CFR Part 210, *Current Good Manufacturing Processing, Packaging, or Holding of Drugs*, current edition Title 21 CFR Part 211, *Current Good Manufacturing Practice for Finished Pharmaceuticals*, current edition 21 CFR Part 312, 21 CFR Part 601, 21 CFR Part 812, and 21 CFR Part 814.

6.1. FDA-regulated research must be coordinated with the FRACCO prior to submission to the AFRL IRB or FDA, including initial submissions and subsequent changes/amendments.

6.2. Sponsors, investigators, and other researcher support staff who manage or conduct FDA-regulated studies must comply with applicable statutes and regulations intended to ensure the integrity of investigational research data and to ensure the protection of the rights, safety, and welfare of human participants enrolled in research studies.

6.3. **Sponsors.** Sponsor may be individuals, institutions or organizations who takes responsibility for the initiation and management of the investigation, but do not actually conduct the investigation.

6.3.1. Sponsors will comply with the responsibilities found in 21 CFR Chapter 1, Subchapter D and H.

6.3.2. Sponsors will select qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring effective monitoring, IRB review and approval are obtained, and the investigation is conducted IAW the general investigational plan and protocols contained in the IND.

6.3.3. Sponsors will submit and maintain an effective IND or IDE application and ensure the FDA, IRB, and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug, device, or biologic product under investigation.

6.4. FDA-regulated research must be submitted to the AFRL IRB for review and approval. Include the following.

6.4.1. Current required institutional documentation as specified by the AFRL IRB.

6.4.2. The Investigator's Brochure, package insert, manufacturing practices and other related documents.

6.4.3. Financial disclosure reports.

6.4.4. Case report forms.

6.4.5. Documented FDA training for all investigators on the protocol, FDA Form 1572, or IDE application.

6.5. **FDA-regulated Exemptions.** The FDA provides provisions for exemptions from some of the regulations and allows for an IRB to provide oversite on certain activities in their stead.

6.5.1. IND Exemptions. An investigation of a drug which meets all the following criteria as defined in 21 CFR Part 312 qualifies for an exemption.

6.5.1.1. The study is not intended to support FDA approval of a new indication for the use of the drug or biologic or a significant change in the product labeling.

6.5.1.2. The study is not intended to support a significant change in the advertising for a lawfully marketed prescription drug product.

6.5.1.3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

6.5.1.4. The study is conducted in compliance with requirements of an IRB and informed consent, as set forth in 21 CFR Part 50 and 21 CFR Part 56.

6.5.1.5. The study is conducted in compliance with 21 CFR Part 312.7, promotion of and charging for investigational drugs.

6.5.2. In Vitro Diagnostic Biologic Product Exemptions. An investigation of an in vitro diagnostic biological product which meets all the following criteria as defined in 21 CFR Part 312 qualifies for an exemption.

6.5.2.1. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.

6.5.2.2. It is labeled stating, “CAUTION: Contains a biological product for investigational in vitro diagnostic tests only” and is otherwise shipped in compliance with 21 CFR Part 312.160.

6.5.2.3. A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirement to submit an IND, if shipped in accordance with 21 CFR Part 312.160.

6.5.3. IDE Exemptions. An investigation of a medical device which meets all the following criteria as defined in 21 CFR Part 812 qualifies for an exemption.

6.5.3.1. A device, other than a transitional device, in commercial distribution immediately before 28 May 1976, when used or investigated IAW the indications in labeling in effect at that time.

6.5.3.2. A device, other than a transitional device, introduced into commercial distribution on or after 28 May 1976, the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before 28 May 1976, and is used or investigated IAW the indications in the labeling FDA reviewed in determining substantial equivalence.

6.5.3.3. A diagnostic device, if the sponsor complies with applicable requirements in FDA regulations and if the testing:

6.5.3.3.1. Is noninvasive.

6.5.3.3.2. Does not require an invasive sampling procedure that presents significant risk.

6.5.3.3.3. Does not by design or intention introduce energy into a subject.

6.5.3.3.4. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

6.5.3.4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

6.5.3.5. A device intended solely for veterinary use.

6.5.3.6. A device shipped solely for research on or with laboratory animals and labeled IAW FDA regulations.

6.5.3.7. A custom device as defined in FDA regulations, unless the device is being used to determine safety or effectiveness for commercial distribution.

6.5.4. In-Vitro Diagnostic (IVD) Device Exemptions. An investigation of an IVD which meets all the criteria as defined in 21 CFR Part 812 qualifies for an exemption. Additionally, the FDA intends to exercise enforcement discretion as to the informed consent requirements for clinical investigators, sponsors, and IRBs if an in-vitro diagnostic device investigation is performed and all of the following are true.

6.5.4.1. The IVD study uses leftover specimens, that is, remnants of specimens collected for routine clinical care or analysis that would have been discarded. The study may also use specimens obtained from specimen repositories or leftover specimens that were previously collected for other research purposes.

6.5.4.2. The specimens are not individually identifiable (i.e., the identity of the subject is not known to and may not readily be ascertained by the investigator, other individuals associated with the investigation, or the sponsor). If the specimen is coded, it will be considered to be not individually identifiable if neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through coding systems.

6.5.4.3. The specimens may be accompanied by clinical information as long as this information does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor.

6.5.4.4. The individuals caring for the patients are different from and do not share information about the patient with those conducting the investigation.

6.5.4.5. The specimens are provided to the investigator(s) without identifiers and the supplier of the specimens has established policies and procedures to prevent the release of personal information.

6.5.4.6. The study has been reviewed by the IRB in accordance with 21 CFR Part 56.

6.5.4.6.1. The AFRL IRB will require the investigators and sponsors to maintain written documentation regarding the factors described above, including the policies and procedures followed by the specimen provider to ensure that the subject cannot be identified. This documentation must be readily made available by investigators and sponsors for FDA review upon request.

6.5.4.6.2. The IRB will inspect this documentation paying particular attention to privacy and confidentiality, and the potential for use of information from the investigation for clinical patient management.

6.6. **Wellness Devices, Software, and Mobile/Wearable Appliances.** The FDA issued final guidance that it does not plan to regulate low risk products that are used to promote/maintain a healthy lifestyle. These products generally are wearable and supported by scientific evidence and associated with low risk to the user. This does not mean the FDA has approved these devices. Devices that are injected, ingested, or invasive would require FDA approval and oversight. The AFRL IRB will review these types of devices per current FDA standards and guidance, which can be found at U.S. Food and Drug Administration (fda.gov).

6.6.1. Software. Software can be a medical device when there is a plan to market the technology. There should be adequate design controls including, software validation, bench testing, and animal testing if applicable. Program Managers, researchers, and sponsors should also be cognizant of potential design control requirements and FDA requirements for software as a medical device and plan for sufficient time in the review and approval process.

6.6.2. Mobile Applications (APP). Mobile APPs can be medical devices. An APP can either be an accessory to an already regulated medical device or used to transform a medical platform into a regulated device. FDA regulates APPs depending on the intended use of the mobile APP and whether it meets the definition of a medical device.

6.7. **Device Risk Assessment.** The regulation governing IDE describes two types of device studies: "significant risk" (SR) and "non-significant risk" (NSR) IAW 21 CFR Part 812.3(m).

6.7.1. A SR device study is defined as a device that presents a potential for serious risk to the health, safety, or welfare of a subject and meets at least one of the following criteria.

6.7.1.1. Is intended as an implant.

6.7.1.2. Is purported or represented to be for a use in supporting or sustaining human life.

6.7.1.3. Is for a use of substantial importance in diagnosing, curing, mitigating or treating a disease, or otherwise prevents impairment of human health.

6.7.1.4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

6.7.2. A NSR device is one that does not meet the definition for a SR study; however, this determination is not synonymous with “minimal risk”.

6.7.3. The effect of the SR/NSR decision is very important to the FDA, research sponsors and investigators. SR device studies are governed by the IDE regulation 21 CFR Part 812. NSR device studies are governed by the abbreviated requirements IAW 21 CFR Part 812.2(b) which includes an IRB serving as the FDA’s surrogate with respect to review and approval of NSR studies.

6.7.4. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination IAW 21 CFR Part 812.150(b)(10).

6.7.5. For both SR and NSR device studies, IRB approval is required prior to conducting the research and for continuing review of the research throughout its lifecycle. Informed consent must also be obtained for either type of study 21 CFR Part 50 or 32 CFR Part 219.

6.7.5.1. IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initial claim of a NSR investigation to the IRB, and if the IRB agrees the device is NSR, it can approve the study for implementation without submission of an IDE application to FDA.

6.7.5.2. If the IRB believes that a device is SR, the investigation may not begin until both the IRB and FDA approve the investigation.

6.8. **Use of Drugs and Medical Devices in Deployed Settings.** Products designated under DoDI 6200.02, *Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs*, for Force Health Protection (FHP) are treatment protocols and not HSR, as no research data and only limited safety data are collected. The U.S. Army Medical Research and Materiel Command (USAMRMC) IRB is designated in DoDI 6200.02 as the reviewing IRB of record for all FHP protocols.

7. Human Research Protection Program (HRPP) Training and Education.

7.1. **HRPP Personnel.** Prior to carrying out HRPP responsibility, institutional personnel involved in the AFRL HRPP will receive human research protection training commensurate with their roles and responsibilities. Unless waived, all required training shall conform to COHRP guidance as made applicable to AFRL IAW DoDI 3216.02_DAFI 40-402.

7.2. **AFRL personnel and others acting under the AFRL DoD Assurance.**

7.2.1. Both initial and ongoing training for AFRL personnel, to include, others acting under the AFRL DoD Assurance, will consist of the designated AFRL modules on the Collaborative Institutional Training Initiative CITI web site or other comparable training as approved by the HPD or AFRL IRB Chair.

7.2.2. The AFRL IRB Chair will include a continuing education topic for IRB staff and members as a standard agenda item at the beginning of each convened IRB meeting. Select AFRL HRPP personnel will complete additional training as required. HRPP personal shall maintain HRPP competencies through profession conferences, certifications, and other professional development opportunities.

7.3. AFRL Support Personnel. Other AFRL divisions/departments who may be involved with identifying and reviewing activity related to human subjects and their data or biospecimens (Gatekeepers) will receive annual HSR briefings provided by the HPD, AFRL IRB Chair, Intramural Lead, or Extramural Lead.

7.4. **Non-AFRL Personnel.**

7.4.1. Other DoD personnel and non-DoD personnel acting under another DoD institution's assurance are required to complete training IAW that institution's HRPP plan. AFRL will not withhold acceptance of that institution's HRPP training as it is presumed compliant.

7.4.2. Non-DoD personnel, acting under a non-DoD assurance, are required to provide evidence of completion of minimally acceptable training. Training shall be taken and will be deemed compliant if completed IAW the non-DoD's institution's HRPP policy.

7.5. Failure of any investigator or key personnel to complete initial and/or ongoing training will render those personnel ineligible to be engaged in or provide support to HSR.

8. Additional Research Related Reviews. In addition to the AFRL IRB and HRPO, there are other levels of research review and approvals required by the DAF and DoD.

8.1. **Scientific Review.** Scientific review ensures the scientific merit of the human research in which an institution is engaged prior to protocol submission to the AFRL IRB. Scientific review is the responsibility of the PI who must work with the reviewer(s) to ensure scientific concerns are appropriately resolved.

8.1.1. Scientific review will be conducted by one or more SMEs free from COIs with the proposed activity. Often a single scientific review does not hold expertise in all areas of the protocol science which must be addressed for effective scientific review. If the protocol includes medical procedures, medical risks, or medically relevant outcomes, at least one of the SMEs should possess the medical knowledge necessary to provide relevant analysis of the protocol.

8.1.2. Scientific Review will ensure the following elements are addressed:

8.1.2.1. The PI and research team are qualified to conduct the proposed research.

8.1.2.2. The research uses procedures which are consistent with sound research design.

8.1.2.3. Interventions and data collection are appropriate for the research and statistical methodology will address the research outcomes and hypothesis.

8.1.2.4. The research design is likely to answer important research questions.

8.1.2.5. The importance of the presumed knowledge, gained from the proposed research, is sufficient to justify the reasonably foreseen risks to participants. The risks are appropriately mitigated ensuring subject safety to the greatest extent possible.

8.1.2.6. The research is based upon thorough knowledge of the scientific literature, including other relevant sources of information as appropriate.

8.1.2.7. The research is feasible and accounts for adequate laboratory space, adequate research support personnel, access to planned study populations and reasonably foreseen experimentation needs during all phases of the activity.

8.1.2.8. Special consideration related to HSR are addressed, including but not limited to FDA requirements, AI ethical principles, and LSGD security.

8.2. The AFRL IRB must consider scientific merit of HSR based on the scientific review provided by the investigator and will determine if the protocol science justifies the use of humans.

8.3. **AFRL Alternate Institutional Official (AIO) Review.** Upon IRB review, the AIO reviews, separate from the IRB process, and determines whether to approve the research. Initial, nonexempt research may not begin until approved by the AIO.

8.4. **Higher Headquarters Review.** The AFRL IRB will identify whether additional human research protection reviews are required prior to initiation and the approval/determination letter will not be released until after the higher headquarters review is completed. Certain activities require timely, coordinated, DAF COHRP approval prior to initiation. DAF COHRP may request modifications or additional information.

8.5. **Artificial Intelligence (AI).** DAF-conducted or -supported HSR (exempt and nonexempt) involving AI enabled tools or capabilities will comply with the DoD ethical principles for AI. per DoDI 3216.02_DAFI 40-402.

8.5.1. AFRL investigators must address these principles within their submission package to the AFRL IRB when the protocol contains elements of AI.

8.5.2. The AFRL IRB or IRB Chair/designee will consider whether these principles are appropriately addressed during the review of AI research.

8.5.3. AFRL-supported research should also address the AI ethical principles in submission to the non-AFRL review authority who oversees the research activity.

8.6. **Large Scale Genomic Data (LSGD).**

8.6.1. Research involving LSGD from DoD-affiliated personnel shall be assessed and approved IAW the security review criteria and procedures of DoDI 3216.02_DAFI 40-402, paragraph 3.10.. For more information on AFRL requirements for genetic/genomic research (See **Attachment 2**).

8.6.2. Research involving LSGD collected from DoD-affiliated personnel will apply an DHHS Certificate of Confidentiality pursuant to Title 42, U.S.C., and Public Law 114-255 and IAW DoDI 3216.02_DAFI 40-402, paragraph 3.10(c).

8.6.2.1. The PI is responsible for obtaining the Certificate of Confidentiality and providing documentation to the AFRL IRB/HRPP.

8.6.2.2. The PI will ensure the Certificate of Confidentiality is applied IAW, DoDI 3216.02, paragraph 3.14(b).

8.6.2.3. Review, Certificates of Confidentiality | Grants & Funding (nih.gov) for further information and to apply.

8.6.3. AFRL security review of LSDG will be completed for protocols by the AFRL IRB Chair or Intramural Lead and forwarded to the DAF COHRP for further approval and coordination.

8.6.3.1. The review will contain an analysis of the LSGD security risks and risk mitigation strategies.

8.6.3.2. The review will also contain recommendations to the final risk categories based on the factual analysis of the protocol as written.

8.6.4. The review will be coordinated with the following subject matter expertise as applicable:

8.6.4.1. The department/division who owns the data or biological samples

8.6.4.2. Bioinformatics and data analytics.

8.6.4.3. Security, privacy, and Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliance.

8.6.4.4. Biosafety.

8.6.4.5. Information Technology.

8.6.4.6. Medical.

8.7. **Biosafety Review.** AFRL will comply with all applicable biosafety and biosecurity requirements for activities pursuant to this issuance; for example: DoD 6055.18-M, the current editions of Centers for Disease Control and Prevention, "Biosafety in Microbiological and Biomedical Laboratories (BMBL)," and the National Institutes of Health guidelines for research involving recombinant or synthetic nucleic acid molecules. Specific requirements for Biosafety can be found at **https://usaf.dps.mil/teams/10213/default.aspx**, and questions may be directed to **711HPW.IR.Biosafety@us.af.mil**.

9. Additional Research Oversight.

9.1. **Research Monitoring.** As appropriate, the AFRL IRB holds authority to compel and approve individualized research monitoring. Such plans are to be documented and directed IAW subject matter expertise and IRB oversight.

9.1.1. The research monitor bears overall responsibility for participant advocacy, however, is not required to personally oversee all elements of data collection. The IRB may designate the specific role of the research monitor in the study.

9.1.2. The IRB will ensure that all identified personnel are appropriately qualified to serve in a specified capacity and that each role is aligned to address a specific research activity and any reasonably-identifiable research risk.

9.1.3. Interaction or intervention with human subjects, to include access to a subject's PII or PHI engaging persons in research, will automatically disqualify such person from serving as a research monitor.

10. Protecting Human Subjects from Medical Expenses.

10.1. When supporting nonexempt human research of greater than minimal risk, AFRL will ensure informed consent documentation for AFRL-conducted or -supported human research includes the following:

10.1.1. Information about medical treatment available for research-related injuries, to include whether any available medical care will be provided free or billed, in whole or in part, to the subject or the subject's insurer.

10.1.2. A statement about whether compensation for research-related injuries is available, and if participating subjects will be in the research work environment as a member of the general public or considered an employee per OSHA 1904.5(b)(2).

10.1.3. A statement that subjects are not waiving legal rights.

10.1.4. A point of contact for further information.

10.2. Human subjects who are DoD healthcare beneficiaries (such as active-duty military personnel or their dependents) are entitled to the same care for research-related injuries within the Military Health System as they would have for any injury or illness IAW DoDI 3216.02_DAFI 40-402.

10.3. **Human subjects who are not DoD healthcare beneficiaries.** Human subjects who are not DoD healthcare beneficiaries and receive treatment outside an MTF will be responsible for any expenses incurred for their treatment IAW DoDI 3216.02_DAFI 40-402.

10.4. Neither the DAF nor AFRL have authority to provide directly, or through third party involvement, compensation for research-related injuries.

11. Adverse Events and Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO).

11.1. For any IRB approved protocol, it is crucial that investigators and research monitors take appropriate steps to promptly recognize, evaluate, and make necessary disclosure of any serious adverse events (SAE) or UPIRTSO. While the research monitor should be closely involved, it is the responsibility of the PI to take all appropriate corrective action and to comply

with reporting requirements. Investigators will promptly (within 5 days) inform the designated IRB and their sponsor(s) of any SAE, UPIRTSO, and of any anticipated adverse event (matter identified in the protocol or informed consent document). Research teams shall remain alert to any unanticipated problem so that the AFRL IRB and/or IRB Chair may timely evaluate such facts to determine if a reportable UPIRTSO did in fact occur.

11.2. **Reporting Timelines.**

11.2.1. Investigators will report UPIRTSOs to the AFRL IRB as soon as possible but in no event shall notification be later than five days from the time of initial recognition.

11.2.2. Investigators will report any UPIRTSO or SAEs to the AFRL IRB as soon as possible but no later than 72 hours from the time of initial recognition.

11.2.3. AFRL will report any UPIRTSO to the COHRP as soon as possible, but within 5 working days of completion of the report.

11.3. AFRL-conducted human research overseen by the AFRL Institutional Review Board (IRB). The AFRL IRB reviews all UPIRTSOs and serious adverse event reports for human research.

11.4. AFRL-conducted human research overseen by a non-AFRL Institutional Review Board (IRB). Report all UPIRTSOs and serious adverse events to the AFRL IRB office IAW the timelines above. The AFRL IRB office reviews all UPIRTSO and serious adverse event reports for human research conducted by AFRL under the purview of a non-AFRL IRB. These reports are reviewed by the HPD or AFRL IRB Chair, who will notify the IO/AIO and DAF COHRP of in a brief but informative documentation clarifying the nature and date of the event, prognosis for the subject, and any corrective action necessary.

11.5. AFRL-supported human research conducted by a non-DoD institution and overseen by a non-AFRL Institutional Review Board (IRB). The AFRL HRPO reviews all UPIRTSO reports for human research under their purview IAW DoDI 3216.02_DAFI 40-402. The HRPO will notify the IO/AIO and DAF COHRP of these UPIRTSOs in a brief but informative documentation clarifying the nature and date of the event, prognosis for the subject, and any necessary corrective action.

11.6. **Other Reporting Requirements for AFRL Investigators.** AFRL investigators may be required to notify the Department/Division Chief or other agencies IAW this instruction and local directorate or organizational guidelines or policies of adverse events or UPIRTSOs, so subsequent reporting and inquiry can be conducted. Investigators are responsible to ensure they know and adhere to these requirements.

12. Noncompliance and Research Misconduct. This section applies to alleged noncompliance or misconduct involving human research.

12.1. AFRL takes seriously every allegation of noncompliance or research misconduct with human research. Each will be investigated in a fair, thorough, and objective manner with every effort to maintain confidentiality of those involved. Allegations will be promptly reviewed and resolved. A climate free of fear of sanction is required to foster appropriate reporting and ensure a fair review of allegations. AFRL will take steps to protect individuals who make good faith allegations of noncompliance with this policy.

12.2. **Noncompliance.** Noncompliance is failure to act (irrespective of intent) IAW the references (See **Attachment 1**) or a deviation from an approved protocol or HRPP determination (e.g., by the IRB or HRPO).

12.2.1. Submit to the AFRL IRB office any allegations of potential noncompliance in human research overseen by the AFRL IRB or conducted by AFRL personnel.

12.2.2. The AFRL IRB Chair (or Chair appointed delegate):

12.2.2.1. Will gather facts to determine whether there was potentially noncompliance.

12.2.2.2. Has authority to determine whether an incident constitutes serious or continuing noncompliance. Will refer all potential serious or continuing noncompliance to the convened IRB.

12.2.3. The PI, Branch Chief, and Division Chief will provide a root cause analysis and proposed corrective actions for the incidence of noncompliance.

12.2.4. IRB Review of Noncompliance. The convened AFRL IRB will:

12.2.4.1. Review all information assembled in the inquiry.

12.2.4.2. Offer the investigator(s), and any appropriate party with material, evidentiary standing, an opportunity to speak at the convened meeting. If in-person presence is not practical, then signed documentary evidence shall be reviewed by the board.

12.2.4.3. Determine whether the noncompliance is serious and/or continuing. Issue requirement and recommendations for necessary corrective action. The AFRL IRB will establish requirements within their purview to control and will recommend to the IO/AIO any other necessary corrective action which includes but shall not be limited to destruction of data, prohibition against publication, and other appropriate personnel action(s).

12.2.5. Notification of Determination. The AFRL IRB Chair/designee will provide the written determination to the investigator(s), their PI (if applicable), the PI's CoC or line of reporting, and the investigator(s) IO/AIO. The determination will describe the nature of the noncompliance and include any corrective action required or recommended.

12.2.5.1. Appeals are conducted pursuant to policy set forth in **paragraph 4.3.15**. Such appeals shall be in writing within five days of the IRB's initial action. Written or in-person delivery of evidentiary matters before the AFRL IRB shall be directed by the IRB Chair.

12.2.5.2. Findings, on appeal, will be provided in writing. Any recommendation(s) to include applicable corrective action, will be made to the investigator(s), PI, and the PI's Branch and Department/Division Chiefs. Additionally, finalized decisions and/or applicable notifications shall include, when appropriate, IO/AIO's additional corrective action.

12.2.5.3. Substantiated serious and/or continuing noncompliance or noncompliance related to classified research will be reported through the IO/AIO to DAF COHRP (which will notify USD[R&E]), other applicable department or agency head(s), officials of the Institution, and funding agencies as soon as possible, within 5 working days of the completed report.

12.2.5.4. Allegations of noncompliance from private citizens will require the information necessary to allow investigation of the allegation, including protocol title, name of investigator, research location, and dates of related research events.

12.2.5.5. For allegations involving a non-DoD institution, the non-DoD institution must conduct an investigation in accordance with the applicable support agreement, to be furnished to the supporting DoD organization via the HRPO. The DoD institution supporting the HSR must ensure in its agreements with the non-DoD institution that allegations are promptly and properly investigated. The DoD institution will then promptly report substantiated serious and/or continuing non-compliance findings to the COHRP.

12.2.5.6. Records. AFRL IRB office will file all records regarding the inquiry of noncompliance (including facts gathered, correspondence, IRB minutes, letters to the investigators, and notification letters to others) in the corresponding protocol file.

12.3. **Research Misconduct.** Research misconduct is the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Allegations of research misconduct will be investigated and resolved IAW 711 HPW OI 61-01, *Research Ethics*.

12.3.1. If the AFRL IRB Chair identifies potential research misconduct during an inquiry of noncompliance, the Chief Scientist, the Department/Division Chief of the investigator(s) involved will be immediately notified.

12.3.2. The Department/Division Chief will notify the AFRL IRB Chair immediately if, following an inquiry, an inquiry of research misconduct is initiated on an investigator. The Department/Division Chief has the responsibility to notify the 711 Wing Commander, Directorate Commander or Director, depending on organizational structure and processes.

12.3.3. The Department/Division Chief will assist the AFRL IRB Chair in determining whether the misconduct harmed or violated the rights of any human subjects. If it is determined subjects were harmed or their rights were violated because of the misconduct, the case will be referred to the AFRL IRB for consideration.

13. Additional Reporting. This section captures reporting requirements not identified elsewhere in this instruction. In addition to the IO/AIO, AFRL will submit, per the HPD's direction, the below events to IOs/AIOs of other institutions, DAF COHRP (which will report to USD[R&E]), IRB Chair(s) of institutions participating in the research, and funding agencies, if applicable.

13.1. **Significant Government Communications.** AFRL will report significant communications regarding AFRL-conducted or -supported human research between the AFRL and other Federal, state, or foreign departments or agencies, including but not limited to all investigations and audits of the Institution's HRPP.

13.2. **FDA-Regulated Events.** AFRL will report to DAF COHRP and the FDA any of the following occurring in human research conducted or supported by AFRL: adverse events associated with use of drugs; 21 CFR Part 312; biologics, Title 21 CFR Part 600, *Biological Products*, current edition or medical devices, 21 CFR Part 812.

13.3. AFRL will report to DAF COHRP any suspension or termination of IRB approval for all activities conducted or supported by AFRL, regardless of the IRB of record.

13.4. AFRL will report to DAF COHRP any other item that must be reported to USD(R&E) and the HPD will maintain clear, consistent, and regular communication with the DAF COHRP during all such activities of reportable interest.

14. Classification Considerations.

14.1. Classified research will comply with the provisions IAW DoDI 3216.02_DAFI 40-402. Contact the AFRL IRB office or HRPO, as appropriate, regarding procedures for communication or submission of any classified information or materials.

14.2. **Communications for Controlled Unclassified Information (CUI).** Not all communications with the AFRL IRB office or HRPO need be CUI. The sender is responsible to comply with applicable regulations, policies, and guidance.

15. Informed Consent. Unless an alternative approach is approved by the IRB, written, legally effective, informed consent will be obtained in advance from all human subjects (or their legally authorized representatives) in nonexempt human research. When ICDs are required to be posted on clinicltrials.gov DAF COHRP will be consulted regarding appropriate redactions.

15.1. Investigators can request waivers or alterations of informed consent and waivers of documentation of informed consent as regulated IAW 32 CFR Part 219. DoD restricts waivers of informed consent for "experimental subjects" IAW references (See **Attachment 1**).

15.2. **Recruitment.**

15.2.1. Federal guidance considers direct advertising for research subjects as part of the informed consent process. All recruitment procedures and materials (e.g., ads, flyers, e-mail, briefings, telephone scripts, etc.) must be reviewed and approved by the IRB.

15.2.2. Advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest.

15.2.3. Recruitment emails must begin with the following statement to convey IRB approval; "The following recruiting announcement is distributed IAW AFRL IRB-approved research protocol FWR20xxxxxx and sent on behalf of the Principal Investigator."

15.3. **Prevention of Coercion.**

15.3.1. When recruiting military subjects, the protocol must identify procedures to prevent coercion and undue influence from superiors. It must be made clear that commanders and supervisors will not be involved in the recruitment or consenting process, and Command authorities will not be made aware of those who consent.

15.3.2. Excluded supervisors or those in the relevant CoC may choose for themselves to participate in separate recruitment sessions. Such sessions are to be coordinated with the research team to comply with the intent of this section.

15.4. **Compensation.** Investigators must comply with the compensation criteria of DoDI 3216.02 regarding DoD-affiliated personal. Potential human subjects must be informed of whether compensation is provided and to what extent. It must be clear there are no plans to provide compensation beyond what's described in the ICD.

15.5. **Inspection Disclosure.** Per DoDI 3216.02_DAFI 40-402, paragraph 3.9a(3) ICDs for DAF-conducted or –supported nonexempt HSR will identify DoD's relationship to the HSR (e.g., as the sponsor) and state the DoD may inspect the research records. This is a DAF interpretation of the requirement of 32 CFR Part 219.116(a)(4).

15.6. DAF-conducted or –supported nonexempt HSR will identify DoD's relationship to the HSR (e.g., as the sponsor) and state the DoD may inspect the research records. This is a DAF interpretation of the requirement of 32 CFR Sections 219.116(a)(4) (on information a reasonable person would want to know) and 219.116(b)(5) (on description of limits to confidentiality). The IRB of record for the HSR has authority to waive or alter this requirement per Section 219.116(f) of 32, CFR (3.9.a.(3)).

16. Protections of Privacy and Confidentiality.

16.1. All parties covered by this instruction, irrespective of the unique role and level(s) of assigned/delegated responsibility, shall not disclose nor attempt to divulge any research-related matters deemed confidential, proprietary, or which may otherwise contain private information to outside parties not identified in the approved research protocol. Requests for official information are covered by confidentiality protections and will be processed IAW standard records release requirements.

16.2. AFRL personnel will protect information related to a subject's participation in research to ensure the privacy of the subject and confidentiality of research data. PII gathered during a research protocol will be kept confidential and only shared with those individuals who have a "need to know" for oversight purposes or as documented in the IRB approved protocol.

16.3. AFRL will comply with AFI 33-332, "Air Force Privacy and Civil Liberties Program," and AFI 41-200, "Health Insurance Portability and Accountability Act (HIPAA)," when applicable to HSR. Either the IRB will include members with this expertise or will seek consultation from the Wing Privacy Officer and/or HIPAA Officer.

16.4. AFRL complies with information security program processes regarding appropriate access control and other protective measures for safeguarding research data in accordance with DoDM5200.01V1_AFMAN16-1404V1, "Information Security Program: Overview, Classification, and Declassification," and DoDI5200.48_DAFI16-1403, "Controlled Unclassified Information (CUI)."

16.5. AFRL uses the following safeguards to protect the physical and electronic security of human research data, when possible: DAF compliant hardware and software, secure storage files, locked rooms with limited access, computer firewalls and passwords for data stored electronically, coding of data with removal of personal identifiers, and use of anonymously collected data.

16.6. AFRL investigators will use the authority pursuant to Sections 501-513 of the Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA) (Public Law 107-347) to assure that data or information acquired by the DoD Component under a pledge of confidentiality for exclusively statistical purposes must 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 CIPSEA Sections 512 and 523-525 and of Volume 72, Federal Register. All proposals to use authority under CIPSEA must have CLAR prior to implementation.

16.7. AFRL personnel will not release research data except as permitted by the IRB approved research protocol unless otherwise required by law or in response to an emergent situation which requires such disclosure to minimize harm to subjects or others.

17. Record Keeping.

17.1. AFRL and investigators from other institutions overseen by the AFRL HRPP will comply with applicable recordkeeping requirements.

17.1.1. Research records will be securely maintained for a term of at least three years after study closure, or IAW other applicable requirements, whichever is longer.

17.1.2. HIPAA related documentation (such as HIPAA authorizations, waivers of authorization, and accounting for disclosure logs) will be maintained for at least six years from the date of completion of the protocol.

17.1.3. Records will be available for inspection by AFRL HRPP personnel and higher headquarters representatives IAW **Attachment 1**.

17.1.4. Investigators will destroy all confidential, personally identifiable data when it is no longer needed for research purposes. Data that has been stripped of all identifiers and all links thereto may be maintained to the extent permitted by the IRB; any subsequent use of such de-identified data will be cleared through the IRB to ensure it is compliant and consistent with any subject permissions provided under the protocol that generated the data.

17.2. **Official Files.** The AFRL IRB office, HRPO, and investigators will maintain proper record keeping for each individual human research activity such as:

17.2.1. The IRB approved protocol and ICD.

17.2.2. All approval letters from the IRB, IO/AIO, and DAF COHRP (where applicable).

17.2.3. Continuing review reports and a final report.

17.2.4. All requested amendments.

17.2.5. Adverse events or UPIRTSOs.

17.2.6. Substantive correspondence between the PI and the AFRL IRB office.

17.2.7. Any Assurance of Compliance approved by DAF COHRP or an IIA where applicable.

17.2.8. Documentation of legal review (where applicable).

17.2.9. Directorate and PI Acknowledgement letters (as applicable per the AFRL HRPP).

17.2.10. Curriculum vitae of investigators.

17.2.11. Electronic copies of subject signed ICDs (as applicable per the AFRL HRP).

17.2.12. Presentations or publications resulting from the research submitted by the PI.

17.2.13. Inquiries of noncompliance to include final outcome.

17.2.14. Any available AFRL IRB minutes for the meeting where the research was reviewed/approved (this does not apply to PIs).

18. Conflicts of Interest.

18.1. **Terms**

18.1.1. A COI 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.

18.1.2. 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 will be evaluated with the same rigor as actual conflicts.

18.2. **Disclosure.** All personnel involved in the conduct or oversight of AFRL supported human research have a responsibility to disclose and eliminate or mitigate any potential COI.

18.2.1. The AFRL IRB Chair will remind members at the beginning of each meeting to declare any COI and recuse themselves from voting where appropriate.

18.2.2. Investigators will notify the AFRL IRB office in writing of a potential COI on any given protocol and include provisions for how they will either eliminate or mitigate their COI.

18.2.3. AFRL HRPOs will not review activities for which they have a COI.

18.3. Any AFRL IRB approved ICD will list all sponsors of the research and any potential COI that has 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:

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

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

18.3.3. Intellectual property rights (e.g., patents, copyrights, and royalties).

18.3.4. Membership on a governing board.

18.4. To avoid a COI, or the appearance thereof, senior members of organizations (e.g., Department/Division Chiefs, their deputies and Branch Chiefs and their Deputies) who are also members of the AFRL IRB will abstain from voting when protocols from their departments/divisions or branches are being presented.

19. Post Approval Compliance Monitoring (PACM).

19.1. All AFRL supported or conducted human research, as well as any human research overseen by the AFRL IRB or an AFRL HRPO, is subject to the Quality Assurance/ Quality Improvement (QA/QI) initiatives of this section. The purpose of the review is to ensure compliance and look for opportunities for process improvement. A roster of all audits of activities under the purview of the AFRL IRB and any findings will be reviewed at the next convened IRB meeting. Any AFRL IRB member or AFRL HRPP personnel can perform a QA/QI review, except where any potential COI exists.

19.2. These audits may be periodic (as part of an ongoing QA/QI program) or for cause. Activities may be selected for periodic audit by individual, organization, category, risk level, etc. For cause audits may be triggered by a materially significant incident (e.g., an adverse event, allegation of a COI, documented complaint of noncompliance, etc.), or per the request of a sponsor or supervisor.

19.3. **Process.** The HPD will assign AFRL HRPP personnel to conduct periodic (at least annually) and for cause audits of a representative sample of activities under the scope of this program.

19.3.1. External. External audits refer to those research activities conducted by PIs and under the AFRL IRB or HRPO prevue. The auditor will ensure compliance with all administrative and regulatory requirements. This audit will include an interview with the PI and study staff, as well as review of investigator records. When warranted, site visits may be deemed necessary. Site visits allow for collection of additional information such as a tour of the research facilities, access to staff, and related observation of the overall research environment to include, when possible, the informed consent process or data collection.

19.3.1.1. The auditor will schedule a time with the PI to conduct the assessment and provide any necessary materials prior to the visit.

19.3.1.2. The auditor will notify the Intramural Lead in writing of any findings or opportunities to improve, who will coordinate responses with the HPD or AFRL IRB Chair as appropriate.

19.3.1.3. The PI will have a chance to respond to and findings and will be notified in writing of any irregular findings, opportunities to improve and/or required corrective actions.

19.3.2. Internal. Internal audits refer to those audits reviewing AFRL HRPP, IRB, and HRPO administrative activities and records. The auditor will notify the Intramural or Extramural Lead in writing of any findings or opportunities to improve, who will coordinate responses with the HPD or AFRL IRB Chair as appropriate.

20. Continuity of Operations.

20.1. This section describes the AFRL HRPP Continuity of Operations Strategy (hereinafter referenced as “Strategy”). It applies in any government closure situation resulting in forced reduction in HRPP personnel, regardless of duration, scope. Its purpose is to maintain AFRL HRPP operations to ensure the safety, rights, and welfare of participants in HSR.

20.2. For closures anticipated to be short (less than thirty consecutive calendar days), the following requirements apply.

20.2.1. The HPD is deemed essential to ensure continuing protection of human subjects in DAF-conducted or -supported HSR.

20.2.2. The HPD will ensure at least one mission essential government employee is sufficient to carry on minimal duties necessary to protect human subjects (e.g., IRB functions, HRPO functions, and reporting of an unanticipated problem involving risks to human subjects or others, as well as serious or continuing noncompliance).

20.2.3. If not possible to maintain staffing, the HPD will seek DAF COHRP direction to refer customers to alternative HRPP office.

20.2.4. The IO will assess whether any ongoing HSR can continue or must stop.

20.2.5. If necessary, the HPD will ensure non-DoD institutions conducting DAF-supported HSR, and subjects in DAF-conducted HSR, are provided appropriate alternate HRPP contacts. If a key investigator or research monitor (when required by the IRB) is furloughed without an alternate, the HSR must stop but only if stopping HSR does not pose a risk of harm to the human subjects.

20.2.6. If protocol deviations are necessary to ensure subject welfare, the PI investigator will get prior IRB approval, if possible. If not possible, report these to the IRB as soon as possible.

20.3. Lengthy closures (e.g., lasting more than 30 calendar days) the preceding provisions above will also be executed, where possible. The HPD will continue to report to the DAF COHRP their plan of action and HRPP status.

20.3.1. The DAF COHRP will assess the plan and respond accordingly (e.g., via acknowledgment with no action necessary) request for additional corrective action, or suspension of the institution’s HRPP.

20.3.2. The DAF COHRP will report to the SDO whether the AFRL HRPP maintains sufficient resources to continue research activities and recommend appropriate courses of action, as needed.

JASON E. BARTOLOMEI,
Brigadier General, USAF
Commander

Attachment 1

GLOSSARY OF REFERENCES AND SUPPORTING INFORMATION

References

Title 21 CFR Part 50, *Protection of Human Subjects*, current edition

Title 21 CFR Part 54, *Financial Disclosure by Clinical Investigators*, current edition

Title 21 CFR Part 56, *Institutional Review Boards*, current edition

Title 21 CFR Part 58, *Good Laboratory Practices for Nonclinical Laboratory Studies*, current edition

Title 21 CFR Part 210, *Current Good Manufacturing Processing, Packaging, or Holding of Drugs*, current edition

Title 21 CFR Part 211, *Current Good Manufacturing Practice for Finished Pharmaceuticals*, current edition

Title 21 CFR Part 312, *Investigational New Drug Application*, current edition

Title 21 CFR Part 314, *Applications for FDA Approval to Market a New Drug*, current edition

Title 21 CFR Part 600, *Biological Products*, current edition

Title 21 CFR Part 601, *Licensing*, current edition

Title 21 CFR Part 812, *Investigational Device Exemptions*, current edition

Title 21 CFR Part 814, *Premarket Approval of Medical Devices*, current edition

Title 29 CFR Part 1635, *Genetic Information Nondiscrimination Act (GINA) of 2008*

Title 32 CFR Part 219, *Protection of Human Subjects*, current edition

Title 45 CFR Part 46, *Protection of Human Subjects*, current edition

DFARS 252, *Protection of Human Subjects*, July 2009

DoDI 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -Supported Research*, 15 April 2020

DoDI 3216.02_DAFI 40-402, *Protection of Human Subjects and Adherence to Ethical*

Standards in Department of the Air Force -*Supported and -Conducted Research*, 17 Jan 24

DoDI 6200.02, *Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs*, 27 Feb 2008

AFI 33-322, *Records Management and Information Governance Program*, 28 July 2021

AFRLI 61-103V2, *AFRL Test Activity Involving Human Participants*, 6 October 2020

711 HPW OI 61-01, *Research Ethics*, 21 October 2022

44 FR 23192, *Belmont Report: Ethical Principals and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, 18 April 1979

Office of the Under Secretary of Defense Memorandum, *Minimum Education Requirements for DoD Personnel Involved in Human Research Protection*, 16 August 2012

Prescribed Forms

None

Adopted Forms

DAF Form 847, *Recommendation for Change of Publication*

FDA Form 1572, *Statement of Investigator*

Abbreviations and Acronyms

ACMG—American College of Medical Genetics and Genomics

AE—Adverse Event

AF—Air Force

AFI—Air Force Instruction

AFRL—Air Force Research Laboratory

AFRLI—AFRL Instruction

AIO—Alternate Institutional Official

APP—Application

BLA—Biologics Licensing Applications

CFR—Code of Federal Regulations

CITI—Collaborative Institutional Training Initiative

CLAR—Component Level Administrative Review

CLIA—Clinical Laboratory Improvement Amendment

COC—Chain of Command

COHRP—Component Office of Human Research Protections

COI—Conflict of Interest

CUI—Controlled Unclassified Information

DFARS—Defense Federal Acquisition Regulation Supplement

DHHS—Department of Health and Human Services

DNA—Deoxyribonucleic Acid

DoD—Department of Defense

EDO—Exempt Determination Official

FD&C—Food, Drug, and Cosmetics

FDA—Food and Drug Administration

FHP—Force Health Protection

FRACCO - FDA—regulated Activities Consultant and Compliance Officer

FWA—Federalwide Assurance

GINA—Genetic Information Nondiscrimination Act of 2008

GCP—Guidelines for Good Clinical Practice

HIPAA—Health Insurance Portability and Accountability Act of 1996

HPD—Human Protections Director

HRPO—Human Research Protection Official

HRPP—Human Research Protection Program

IAIR—Institutional Agreement for IRB Reviews

IAW—In accordance with

ICD—Informed Consent Document

ICH—International Conference on Harmonization

IDE—Investigation Device Exemption

IIA—Individual Investigator Agreement

IND—Investigational New Drug

IO—Institutional Official

IR—Institutional Research

IRB—Institutional Review Board

IVD—In-Vitro Diagnostic

MRI—Magnetic Resonance Imaging

NDA—New Drug Application

NSR—Non-significant Risk

OHRP—Office of Human Research Protections

OPR—Office of Primary Responsibility

PCS—Permanent Change of Station

PI—Principal Investigator

PII—Personally Identifiable Information

PHI—Protected Health Information

PMA—Premarket Approval Application

PRIM&R—Public Responsibility in Medicine and Research

QA—Quality Assurance

QI—Quality Improvement

SAE—Serious Adverse Events

SG—Surgeon General

SOP—Standard Operating Procedure

SR—Significant Risk

USAMRDC—U.S. Army Medical Research and Development Command

USD(R&E)— Undersecretary of Defense for Research & Engineering

UPIRTSO—Unanticipated Problem Involving Risk to Subjects or Others

WGS—Whole Genomic Sequencing

Office Symbols

AF/SG—AF Surgeon General

AFRL/CC—AFRL Commander

711 HPW/CC—711 HPW Commander

711 HPW/DD—711 HPW Deputy Director

711 HPW/IR—711 HPW Institutional Research

Terms

AE—Adverse event. Any untoward or unfavorable medical event or occurrence (physical or psychological) in a human subject, including any abnormal sign (e.g., abnormal physical examination or laboratory finding), symptom, or disease, temporarily associated with the subject's participation in the research.

American College of Medical Genetics and Genomics—The ACMG is a nationally recognized interdisciplinary professional membership organization that represents the interests of the entire medical genetics team including clinical geneticists, clinical laboratory geneticists, and genetic counselors.

Alternate Institutional Official—A person to whom the IO has delegated authority and responsibility to fulfill the IO's duties for the purposes of overseeing the institution's HRPP.

Biologics Licensing Applications—The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by any legal person or entity who is engaged in manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards.

CITI—Collaborative Institutional Training Initiative provides education and training on ethics, research, meeting regulatory requirements, responsible conduct of research, research administration and other topics pertinent to the interests of member organizations, individual learners, and society.

CLAR—Component Level Administrative Review is a special review performed by the DoD Component Office for certain classes of research that have additional regulatory requirements and considerations such as research in a foreign country.

CLIA—Clinical Laboratory Improvement Amendments are federal regulations that establish quality standards for laboratories in the United States that test human specimens to ensure that patient test results are accurate, reliable, and timely.

COHRP—Component Office of Human Research Protections establishes policies and procedures, and provides education and training related to DAF Human Research Protection Programs (HRPPs). This office also ensures the compliance of human research reviews after institutional review board approval and performs site visits at random or for cause audits.

DFARS—Defense Federal Acquisition Regulation Supplement is a set of regulations that apply to all U.S. Department of Defense (DoD) contracts and subcontracts, designed to ensure that the DoD receives quality goods and services at fair and reasonable prices.

DNA—Deoxyribonucleic Acid is a molecule that contains the genetic information that controls the growth, development, and reproduction of organisms.

FDA—Food& Drug Administration is a US federal agency that protects public health by regulating the safety of a variety of products and services

FD&C Act—Food, Drug, and Cosmetics Act is a set of laws passed by the United States Congress in 1938 giving authority to the U.S. Food and Drug Administration to oversee the safety of food, drugs, medical devices, and cosmetics.

FWA—Federalwide Assurance is a document that demonstrates an institution's commitment to following federal regulations that protect human subjects in research.

GCP—Guidelines for Good Clinical Practice is a set of international guidelines that ensure the safety, integrity, and quality of clinical trials that involve humans.

HIPAA—Health Insurance Portability and Accountability Act of 1996 is a federal law that protects health information and regulates its use and disclosure.

HRPP—An institution’s system of interdependent elements that implement policies and practices to protect human subjects involved in research. The purpose of the Human Research Protection Program is to identify, and protect the safety, rights, and welfare of human subjects in, research conducted or supported under the organization’s purview.

Human Subject—A living individual about whom an investigator (whether professional or student) conducting research: Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or Obtains, uses, studies, analyzes, or generates identifiable private information, personally identifiable information, or identifiable biospecimens.

ICH—International Conference on Harmonization an organization that aims to ensure the safe and effective development of medicines by harmonizing the technical requirements for their registration.

IDE—Investigation Device Exemption allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.

IND—Investigational New Drug is a request from a clinical study sponsor to obtain authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

Institutional Official—An institution's senior person who is legally authorized to represent the institution and who is authorized to establish and is responsible to maintain the HRPP for the institution. The IO is responsible for the institution's DoD or federal assurance and IRB, if these elements are part of the institution's HRPP.

IRB—Institutional Review Board is a committee that reviews research studies involving human subjects to ensure they meet ethical standards, comply with regulations, and protect participants. IRBs are also known as independent ethics committees, ethical review boards, or research ethics boards. They are typically located at the site of the research study. IRBs have the authority to approve, disapprove, exempt, monitor, and require modifications to research.

IVD—In-Vitro Diagnostic is a test that analyze samples from the human body to detect diseases, conditions, and infections.

NDA—New Drug Application is a request from a pharmaceutical company to the U.S. Food and Drug Administration (FDA) to market a new drug in the United States.

NSR—Non-significant Risk does not pose a serious risk to human subjects. Examples of NSR devices include Most daily-wear contact lenses and lens solutions, Ultrasonic dental scalers, Foley catheters, Low-power lasers for treatment of pain, and Caries removal solution.

PI—Principal Investigator is the lead researcher and person in charge of a research project or grant, such as a clinical trial or laboratory study.

PMA—Premarket Approval Application is the FDA's process for evaluating the safety and effectiveness of Class III medical devices.

Research—A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this issuance, whether or not they are conducted or supported under a program that is considered research for other purposes.

SAE—Serious Adverse Event (SAE). In the context of a research-induced outcome, the term "serious" means an event that results in death; is life threatening; requires inpatient hospitalization (or prolongation thereof); results in persistent or significant disability/incapacity; results in a congenital anomaly; requires intervention to prevent permanent impairment/damage; or any other event that may seriously jeopardize the subject's health.

SR—Significant Risk is a potential harm to a study participant that could be serious, including the possibility of life-threatening consequences, permanent impairment of bodily function, or the need for substantial medical intervention to prevent such harm.

UPIRTSO—Any incident, experience, or outcome that meets all three of the following conditions:

1—Is unexpected (in terms of nature, severity, or frequency) given the procedures described in the HSR protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied.

2—Is related (or possibly related) to participation in the HSR. In this issuance, "possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by HSR procedures.

3—Suggests that the HSR 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 occurred.

WGS—Whole Genome Sequencing is a laboratory procedure that determines the order of nucleotides in an organism's DNA sequence. It can be used to analyze the DNA of bacteria, viruses, fungi, plants, and animals.

Attachment 2

REQUIREMENTS FOR GENETIC RESEARCH

A2.1. Background.

A2.1.1. Genetic Testing.

A2.1.1.1. Genetic research is broadly defined as research that collects genetic data and/or genetic bio-samples. Although there are not clear boundaries, there are two general categories of genetic research clinical and operational. Clinical genetic research is focused on prediction and prevention of disease while operational genetic research is focused on prediction and enhancement of performance.

A2.1.1.2. Genetic Tests are analysis of human deoxyribonucleic acid (DNA) that detects genotypes, mutations, or chromosomal changes, often used in human subject research. Whole Genomic Sequencing (WGS) is a genetic test for the entire genetic code of an organism that can be used for research or clinical diagnostics.

A2.1.1.3. Special aspects of genetic testing in HSR must be considered in AFRL sponsored programs.

A2.2. Incidental Findings/Secondary Findings.

A2.2.1. Incidental findings are discoveries of individual-level findings that are unrelated to the goals of the study. Various tests, procedures, and evaluations may be performed for non-medical purposes to help a researcher test a hypothesis. An “incidental finding” may be discovered that is unrelated to the research but may be medically important to the human subject’s health. No all-inclusive list of clinically relevant conditions can be generated a priori for a research study. Thus, incidental findings are not directly evaluated but are discovered during research/data analysis. Examples include finding an indication of lung cancer in an X-ray done to look for tuberculosis for research exclusion criteria, finding a brain aneurysm during a Magnetic Resonance Imaging (MRI) conducted for brain mapping purposes, or the discovery of a genetic marker unrelated to the goals of the study. Incidental findings can occur in both Clinical research and non-Clinical research. Not all incidental findings negatively impact the individual and are reportable. In fact, many incidental findings are "unremarkable" or not a source of concern. In the context of active-duty military members and their command(s), ethical principles could be at odds in the reporting of impactful incidental findings of HSR. From one perspective, the human subject can either receive significant health benefit from learning about incidental findings from studies performed for research purposes or experience potential harms including stress, anxiety, and risks due to unnecessary procedures resulting from research data being taken as clinically valid.

A2.2.2. Secondary findings are additional result(s) actively sought by the practitioner or researcher that are not the primary target of the test or procedure. Secondary findings might be deliberately sought when recommended by an expert body or by a consensus of practitioners. For example, the American College of Medical Genetics and Genomics (ACMG) provides a list of genes that clinical laboratories conducting exome/genome sequencing should evaluate for pathogenic mutations because identification prior to phenotypic expression of the associated medical condition(s) has the potential for preventing disease morbidity and mortality.

A2.3. Requirements.

A2.3.1. Military members, when enrolled in genetic studies, shall be considered a vulnerable population. The AFRL IRB shall direct its oversight accordingly.

A2.3.2. Since genetic revelations are often confusing and anxiety-provoking, the AFRL IRB shall ensure that genetic counseling is available when appropriate.

A2.3.3. To date, although genetic biomarker identification for tracing ancestry and sport proclivity has generated serious marketing efforts, they have garnered little scientific support. Until such scientific support exists, the AFRL genetic biomarker research shall make no such selection claims.

A2.3.4. Most authorities favor disclosure of incidental findings. The AFRL IRB shall confirm that procedures for dealing with incidental findings are delineated.

A2.3.4.1. Genetic testing should not intentionally mask/hide data to prevent researchers from receiving important findings of human subjects.

A2.3.4.2. HSR protocols must include an "incidental findings" reporting strategy for genetic testing that clearly describes the genetic markers that are considered returnable as incidental findings.

A2.3.4.3. The researcher is not required to screen all samples for the ACMG list of clinically important genetic markers because these would be secondary findings that are not required in genetic research per this memorandum.

A2.3.4.4. Incidental genetic findings described in the research protocol and discovered during the conduct of research will be reported to both the military human subject and a qualified medical professional credentialled at a DoD or U.S. based hospital for the interpretation and counselling of the incidental finding of interest where Clinical Laboratory Improvement Amendment (CLIA) certified testing may be required at clinical discretion of the provider. Civilian human subjects will be notified of an incidental finding, and 711 HPW will not report these data to any clinical health provider. Researchers will not pursue clinical grade diagnostic testing for the purpose of validating incidental findings.

A2.3.4.5. Exclusion criteria for genomic human protocols involving identifiable data (i.e., when the participant identity is known to the principal investigator) will include any subject who elects to not receive incidental genetic findings. For military human subjects, exclusion may result if the subject elects to not allow data release of incidental findings to an appropriate medical professional credentialled at a DoD or U.S. based hospital for the interpretation and counselling of the incidental finding of interest.

A2.3.4.6. For studies that use de-identification (i.e., when the participant identity is not known to the principal investigator) of biospecimens, and re-identification is not possible, the human subject will not be notified of incidental findings because researchers do not have a means to link the biospecimen and the identity of the human subject.

A2.3.4.7. PIs are allowed to release results of genetic research data to the human subjects unless the IRB directs them otherwise. Release must follow study protocol for incidental findings release.

A2.4. Informed Consent Requirements.

A2.4.1. The informed consent document shall be specific and inclusive. It will include, but will not necessarily be limited to, the following:

A2.4.1.1. The difference between research and clinical genetic testing, and a description of the impacts and relevance of each.

A2.4.1.2. Personal consequences will be detailed to include the psychological, insurability, and employability impact of genetic revelations.

A2.4.1.3. Familial consequences will be similarly detailed. Third party identification aspects of the research will also be addressed.

A2.4.1.4. Data storage, genetic data repositories and genetic specimen biobanks will be described in detail. PII protection will be addressed as well as de-identification procedures.

A2.4.1.5. Data repository descriptors will focus on de-identification procedures, secondary data release (aka data sharing), and future research use of the data.

A2.4.1.6. Biobanking descriptors will focus on de-identification procedures, secondary specimen use (aka specimen sharing), future research use of the specimen, and tissue rights.

A2.4.1.7. Privacy and confidentiality will address what is revealed and to whom it is revealed. In addition, mechanisms to assure protection of subject privacy and data confidentiality will be fully described.

A2.4.1.8. Opt-Out Option (aka subject may decide not to know the results from the study) will be considered and the reasons for or against its use will be enunciated.

A2.4.1.9. The risks of incidental findings occurring in the study.

A2.4.1.10. The legal protections in place to protect the privacy of any incidental finding elucidated during this research (e.g., identify whether Title 29 CFR Part 1635, *Genetic Information Nondiscrimination Act (GINA) of 2008*, current edition applies for this human subject).

A2.4.1.11. The potential career risks to a human subject from an incidental finding.

A2.4.1.12. The reporting requirements for the researcher, human subject, and medical provider who become aware of this incidental finding.