DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
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FCMR-UWZ (1200B) 10 April 2024

MEMORANDUM FOR All Personnel, Walter Reed Army Institute of Research (WRAIR)

SUBJECT: WRAIR Policy #25, Determination that an Activity is Research Involving Human Subjects

1. References.

a. Armed Forces, 10 United States Code (U.S.C.) § 980, (2017).

b. Armed Forces, 10 U.S.C. § 1102, (2017).

c. National Defense, 32 Code of Federal Regulations (C.F.R.) §§ 219.101-219.124, (2018).

d. Public Welfare, 45 C.F.R. §§ 46.101-46.124, (2018).

e. Department of Defense Directive (DODD) 5141.02 (Director of Operational Test and Evaluation (DOT&E)), 2 February 2009.

f. DODD 6025.13-M (Medical Quality Assurance (MQA) and Clinical Quality Management in the Military Health System (MHS)), 17 February 2011.

g. Department of Defense Instruction (DODI) 3216.02 (Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research), 29 June 2022.

h. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research), 1979.

i. U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP) (Guidance on Engagement of Institutions in Human Subjects Research), 16 October 2008.

j. Army Regulation (AR) 70-25 (Use of Volunteers as Subjects of Research).

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*This supersedes WRAIR Policy #25, dated 27 January 2022.

k. Memorandum, Secretary of the Army (SA) (Army Policy for Use of Human Cadavers for Research, Development, Test and Evaluation, Education or Training), 20 April 2012.

l. U.S. Army Medical Research and Development Command (USAMRDC) Policy 21 (Administrative Oversight Review and Approval of USAMRDC Conducted and Supported Human Subjects Research).

m. USAMRDC Policy 78, (Use of Human Cadavers for Research, Development, Test and Evaluation, Education, and Training).

n. WRAIR Policy #24 (Submission Requirements for Human Subjects, their Information or Biospecimens).

o. WRAIR Policy #27 (Submission and Review Requirements for WRAIR Human Cadaver Use).

p. WRAIR Policy #32 (Use of Existing Human Information and/or Biospecimens).

q. WRAIR Policy #33 (Public Health Activity Determination and Oversight Requirements).

2. History. This policy is being issued in accordance with WRAIR and USAMRDC requirements and is effective upon signature by the WRAIR Commander. This version of the policy includes updates with regard to entomological human landing studies, requirements for provision of samples/data, as well as minor editorial and administrative changes. This version of the policy is effective immediately and shall remain in effect until rescinded or superseded in writing, or when it exceeds its expiration on 10 April 2026.

3. Purpose.

a. Clarify what constitutes “research involving human subjects” in accordance with the above references, and

b. Outline the general process within the WRAIR for making this determination.

c. This policy is intended to ensure that a description of any activity within the WRAIR that may be considered “research involving human subjects” is sent to the Human Subjects Protection Branch (HSPB) for a determination and that the determination is not made by investigators.

d. This policy applies to all projects conducted under the WRAIR Human Research Protection Program (HRPP).

Note: Refer to WRAIR Policy #32, Use of Existing Human Information and/or Biospecimens, for requirements associated with research projects that use existing (on-the-shelf) human information and/or biospecimens.

4. Definitions.

a. Anonymized: For the purposes of this policy, “anonymized” refers to coded information or biospecimens, for which the key or link to decipher the code has been destroyed.

b. Anonymous: For the purposes of this policy, “anonymous” refers to information or biospecimens, for which no identifying private information was initially collected.

c. Broad consent: Broad consent is an alternative to study-specific informed consent and applies only for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes).

d. Cadaver: A deceased person or portion thereof, and is synonymous with the terms "human cadaver" and "post-mortem human subject" (PMHS). The term includes organs, tissue, cells, eyes, bones, arteries or other specimens obtained from an individual after death. The term "cadaver" does not include portions of an individual person, such as organs, tissue or blood, that were removed while the individual was alive (for example, if a living person donated tissue for use in future research protocols, that tissue is not considered a "cadaver" under this policy, regardless of whether the donor is living or deceased at the time of tissue use).

e. Coded: Coded is defined in *OHRP Guidance on Research Involving Coded Private Information or Biologic Specimens* as:

(1) Identifying information (for example, name, initials, social security number, address, etc.) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or biospecimens pertain has been replaced with a number, letter, symbol, or combination thereof (such as, the code); and

(2) A key or link to decipher the code exists, enabling linkage of the identifying information to the private information or biospecimens.

(3) Private information or biospecimens are considered to be *individually identifiable* when the identity of the subject is or may readily be ascertained by any member of the research team or management of that research team or is associated with the biospecimen.

f. Existing human information and biospecimens: For the purposes of this policy, existing information and biospecimens means human information and biospecimens that remain after a study is conducted (whether at WRAIR or through collaborative efforts) where all planned analyses and study participant follow-up has been completed. This includes existing information and biospecimens from past research studies, public health efforts, clinical discards, service samples, etc.

g. Future use: For the purposes of this policy, future use means use not covered under a currently open and Institutional Review Board (IRB)-approved protocol. Information/biospecimens must already exist.

h. Human subject: A living individual about whom an investigator (whether professional or student) conducting research: (i) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

i. Identifiable biospecimen: A biospecimen for which the identity of the subject is or may readily be ascertained by any member of the research team or management of that research team, or is associated with the biospecimen.

j. Identifiable private information: Private information for which the identity of the subject is or may readily be ascertained by any member of the research team or management of that research team, or is associated with the information.

k. Interaction: For the purposes of this policy, interaction includes communication or interpersonal contact between investigator and subject.

l. Intervention: For the purposes of this policy, intervention includes both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

m. Official tasker or request: An obligating document detailing a requested activity, which originates from a Command-level authority, is routed through appropriate channels and receives official support from the WRAIR Commander. Generally, requests for WRAIR's services are filtered through USAMRDC, who then contacts WRAIR Headquarters.

n. Research: A systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge.

o. Research involving human subjects: Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve

a living individual about whom an investigator conducting research (i) obtains information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens, or (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

p. WRAIR point of contact (POC): An individual, affiliated with WRAIR or its Directorates, who is responsible for submission of protocol documents to the HSPB over the lifecycle of the study as new protocol actions are processed, remains in continual communication regarding the study to regulatory authorities, and directs study execution wherein WRAIR is participating. This individual is generally the lead WRAIR investigator on the protocol, but is not the overall study Principal Investigator (PI). The POC can be the site PI, a clinical coordinator, program manager, associate investigator, or other individual involved in the study in a scientific, academic or administrative capacity.

5. Determination of the Applicability of 32 C.F.R. §§ 219.101-219.124. The determination that an activity is or is not "research involving human subjects" will be made solely by the HSPB or the WRAIR IRB Chair/Designee. Investigators are encouraged to contact the HSPB before initiating the proposed activity (see WRAIR Policy #24, Submission Requirements for Human Subjects, their Information or Biospecimens, and the Procedure section below for requirements). If a determination is made that an on-going project constitutes human subjects research, the WRAIR IRB cannot grant retrospective approval for that research (see SOP UWZ-C-606, Non-Compliance Procedures).

6. Execution.

a. The PI or WRAIR POC will submit a brief written description of the proposed activity to include an explanation of why the effort, in his/her opinion, does or does not constitute "research involving human subjects" and applicable supporting documentation (for example, Center/Branch/Directorate Director's memorandum, protocol, appropriate training, etc.) to the HSPB mailbox (in Microsoft Outlook Global Addresses: USARMY Ft Detrick MEDCOM WRAIR Mailbox HSPB or usarmy.detrick.medcom-wrair.mbx.hspb@health.mil).

b. Templates and guidance on preparing the submission may be obtained by contacting the HSPB at 301-319-9940 and usarmy.detrick.medcom-wrair.mbx.hspb@health.mil, or by visiting WRAIR's intranet.
(see WRAIR Policy #24, Submission Requirements for Human Subjects, their Information or Biospecimens).

c. For all submissions using existing biospecimens and data, wherein the biospecimens and/or data are coded, anonymized or anonymous, a cover memo and request form/checklist are to be used (refer to Appendix B of the WRAIR Policy #32,

Use of Existing Human Biological Specimens and/or Human Data). Overseas Directorate Directors can opt to use the form in Appendix B of WRAIR Policy #32 as supplemental, since host nations may require a full protocol submission. The Directorate's plan should be discussed with HSPB.

d. The submission will be evaluated by the Exemption Determination Officials (HSPB Director, IRB Chair, or a designee) for a determination on whether:

(1) The activity is either "research" or "not research" (NR) in accordance with 32 C.F.R. § 219.102(l).

(2) If research, the activity is either "involving human subjects" or not, in accordance with 32 C.F.R. § 219.102(e).

e. If it is determined that an activity is "not research" (such as, public health, clinical care, quality assurance), an email acknowledgment of the project or a signed, written document will be provided to the submitting investigator. Even if "not research", The PI (or WRAIR POC) is responsible for obtaining other applicable approvals (for example, USAMRDC Office of Human Research Oversight's (OHRO's) Human Research Protection Official (HRPO) approval) and agreements (for example, Cooperative Research and Development Agreement (CRADA)-Materiel Transfer Agreements (MTAs), Memorandum of Agreement (MOA), import permits, etc.) prior to work on and/or shipment of any human information and/or biospecimens.

f. If it is determined that the activity is "research not involving human subjects" (NHSR), the HSPB will provide the investigator with a written determination for the project. As stated above, the PI (or WRAIR POC) is responsible for obtaining other applicable approvals (for example, USAMRDC OHRO approval) and agreements (for example, CRADA-MTAs, MOA, import permits, etc.) prior to work on and/or shipment of any human information and/or biospecimens.

Note: The HSPB may independently review the labeling of information and/or biospecimens to verify the NHSR or NR determination, as well as, business agreements, as part of post-approval compliance monitoring. For NHSR projects, if WRAIR is the PI/Lead *vs.* a secondary collaborator, a decision will be made on a case-by-case basis on whether local institutional approvals or determinations are required prior to issuance of acknowledgments/determinations. When WRAIR is not the lead of the project, local institutional approvals or determinations are required prior to issuance of acknowledgments/determinations.

g. If the activity is determined to be research involving human subjects, a protocol and IRB review will be required. For submission guidance, refer to WRAIR Policy #24, Submission Requirements for Human Subjects, their Information or Biospecimens. Once a complete submission is received by HSPB, the protocol will be forwarded to the

WRAIR Chief Science Officer and Chair, WRAIR Scientific Review Committee, if applicable, for compliance with scientific review requirements (see Scientific Review of Human Subjects Research Protocols SOP UWZ-002).

Note: With the HSPB Director's approval, informal feedback from HSPB on the submission of a human subjects research protocol can be provided to the investigator as a consultation, on a case-by case basis, but will not take precedence over complete, official submissions.

h. An activity that began as "not research" may change or evolve into research. Or, an activity that began as exempt or NHSR may change or evolve into research involving human subjects. In these cases, WRAIR IRB review and approval is needed before the proposed research activity involving human subjects commences. Under no circumstances can the WRAIR IRB provide retrospective approval of research involving human subjects. The following modifications to these projects must be submitted to the HSPB for an updated review determination to ensure that the changes have not upgraded the risk level determination:

(1) A change in study objectives,

(2) A change in the roles/responsibilities of WRAIR investigators,

(3) A change in the source of samples/data,

(4) A change in funding, or

(5) Investigator access to information that could identify individual donors.

The updated review determination will generally be in the form of an email acknowledgment, if the risk level remains unchanged and no additional regulatory approvals are needed.

7. Examples of Activities that require the HSPB to determine whether they are Research or Research Involving Human Subjects.

a. Quality assurance: This refers to activities such as those carried out under 10 U.S.C. § 1102. and DODD 6025.13, Medical Quality Assurance (MQA) and Clinical Quality Management in the Military Health System, dated effective 29 October 2013. Generally, official taskers are needed for this type of project, as well as, a project summary outlining WRAIR's roles and responsibilities.

b. Program evaluation: Activities that attempt to measure the effectiveness of established DOD or other governmental programs or services with the goal of improving

the program. These activities may also be called quality improvement, performance improvement, or program improvement.

c. Operational test and evaluation: This refers to categories in DODD 5141.02, Director of Operational Test and Evaluation (DOT&E), 2 February 2009. The categories are defined as: “The field test, under realistic conditions, of any item (or key components) of weapons, equipment, or munitions for the purpose of determining the operational effectiveness and operational suitability of the weapons, equipment, or munitions for operational use, including combat, by typical military users, and the evaluation of the results of such test.”

d. Consultation: Includes activities conducted to support the overall protocol concept and design, performance of specific laboratory support, statistical analysis and interpretation of aggregate results, etc. Investigators/WRAIR POCs are encouraged to seek guidance from the WRAIR HSPB before engaging in this type of activity.

e. Storage or maintenance for secondary research for which broad consent is required: Includes the storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the required determinations.

f. Secondary research for which broad consent is required: Includes research involving the use of identifiable private information or identifiable biospecimens for secondary research use, and must meet the following criteria: (1) broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained; (2) documentation of informed consent or waiver of documentation of consent was obtained; (3) a determination is made that the research to be conducted is within the scope of the broad consent; and (4) the investigator does not include returning individual research results to subjects as part of the study plan.

g. Research using coded or anonymous/anonymized private information or human biological biospecimens: See also Section 4, Definitions, of this policy and WRAIR Policy #32, Use of Existing Human Information and/or Biospecimens. Research that involves coded or anonymous/anonymized private information or biospecimens requires a written determination from the HSPB as to whether that activity constitutes human subjects research. Coded private information or biospecimens are considered not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, research involving only coded private information or biospecimens is considered to not involve human subjects as defined under 45 C.F.R. § 46.102(e) if the following conditions are both met:

(1) The private information or biospecimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

(2) The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or biospecimens pertain because, for example:

(a) The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;

(b) There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

(c) There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

(3) This policy applies to existing private information and biospecimens, as well as to private information and biospecimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or biospecimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of biospecimens for a tissue repository.

Note: It is a best practice that the holder of the key/link not work for any investigators listed on the project, as this is a conflict of interest which could result in a breach of confidentiality. If there is no alternative, a documented process may be by approved (on a case-by-case basis) by the HSPB or the WRAIR IRB, which could allow for a department staff member to maintain the key if specific safeguards are in place.

h. Research involving primary cell culture: The growth of cells isolated from a piece or pieces of tissue (explants) taken directly from a living person. This may be biopsy material. Many of the explanted cells will only survive for one or a few passages before dying. (For example, they are not transformed.)

i. Research on human DNA, RNA, proteins, or metabolites: Research on human genetic, genomic, or post-genomic material. Genetic material involves investigations of individual genes and their role in inheritance; genomics involves large scale studies of all genes and their interactions, and post-genomics describes the -omic sciences which have evolved post sequence of the human genome inclusive of nutrigenomics, metabolomics, transcriptomics, and proteomics.

(1) Examples of the above include investigations using DNA, RNA, chromosomes, proteins, or metabolites that can detect sequence changes, genotypes, , or chromosomal changes such as DNA fingerprinting, Genome Wide Association Studies (GWAS), single nucleotide polymorphism (SNP) analysis, DNA/RNA sequencing, transcriptional profiling by PCR array or microarray formats.

(2) Human microbiome research, while not necessarily human genetic research, takes advantage of advances in DNA sequencing technologies to create a new field of metagenomics. This field allows for analysis of genetic material derived from complete microbial communities harvested from natural environments in the human body. Risks associated with such research are similar to the risks associated with inappropriate release of information contained in medical records; therefore, consultation with the WRAIR HSPB is recommended before engaging in this type of research.

j. Research with Cadavers: There are additional oversight requirements for these activities. Refer to WRAIR Policy #27 and USAMRDC Policy 78. This would include research involving autopsy material and/or biological biospecimens or private information from deceased individuals.

k. Entomological studies: This is a change from the previous policy. This includes basic and applied research, field testing, and product development activities where a human serves solely as a lure and/or the use of repellents, pesticides, prophylactic treatment or other products and which may or may not be registered with the US Environmental Protection Agency (EPA). While not strictly covered under “the Common Rule,” given this unique area of study, the WRAIR is opting to include these projects under the WRAIR IRB’s purview for review and approval, where appropriate. These activities may also require Safety and Occupational Health reviews/assessments.

l. Public Health Epidemiological Consultations (EPICONs): Activities (consultations or incident investigations) conducted in response to taskers or requests from outside WRAIR most commonly addressing the epidemiology of infectious diseases and/or behavioral patterns. EPICONs should not be delayed awaiting a determination; however, no research aspects may occur until a determination or IRB approval is received. EPICON project submissions are required within 10 days of the start of the activity (refer to WRAIR Policies #24 and/or #32, as applicable).

(1) If the examples referenced above are Command-directed or public health activities, a determination from the HSPB is still required, as is an official tasker detailing WRAIR’s roles and responsibilities (refer to WRAIR Policy #33, Public Health Activity Determination and Oversight Requirements).

(2) All of the above activities may still require corresponding business agreements. Please seek guidance from the Technology Transfer Office (TTO).

m. Provision of samples/data: While sending samples and data to a collaborating 3rd party is not routinely considered a research activity, unless the WRAIR will be receiving information in return, DoDI 3216.02 requires local regulatory approvals or determinations of receiving institutions be collected and confirmed. Provision is considered "support/assistance" and HSPB is required to confirm the appropriate approvals have been obtained by the recipient. Original intent and usage allowances, as well as, original collaborator permissions, will also be considered. Corresponding business agreements are also required. Please see the TTO.

8. Examples of Activities which Do Not Require a Determination by the HSPB.

a. Pooled biospecimens: Pooled products, such as pooled sera, plasma, cells, or coagulation factors may be used in research without a submission to the HSPB (32 C.F.R. §§ 219.101-219.124 does not apply), as no code or personal identifier would exist for such products. Participants' expressed allowances should still be followed; for example, if a participant stated he/she/they did not want their specimens used outside of the original protocol, the samples should be excluded from pooling as well.

b. Command-Directed non-research activities: These activities must not qualify as research per 32 C.F.R. §§ 219.101-219.124. The activity must be defined per an official tasker without any research elements. If any portion of the activity qualifies as research, a project/protocol must be submitted to WRAIR HSPB for review/determination prior to initiation of work. Any future use of data collected from a Command-Directed non-research activity must be submitted to the WRAIR HSPB for review/determination prior to use. Ideally, permission from participants should be sought for future research use of the data wherever feasible.

c. Research involving established cell lines (for example, HeLa, 3T3, MDCK): These types of cells have an unlimited proliferation capacity. They originated from tumors, transformed cells, etc. and are not individually identifiable (This does NOT include primary cell cultures. See 7.e. above.)

d. Commercially available biological materials: The use of commercially purchased human biological materials unaccompanied by identifiable data (for example, cannot be linked to the donor), does not meet the definition of research involving human subjects. In this case, the commercial company must have a statement that no identifying information will ever be provided to the recipient organization/person. Refer to WRAIR Policy #24 and USAMRDC Policy 78 for requirements associated with the use of cadaveric samples.

e. Isolates: This would include viral, bacterial, or parasitological isolates maintained independently (not in human sera, mucosal swabs, or other human biological materials-unless commercially available see d. above) and unaccompanied by coded or identifiable human data.

9. Non-Compliance. The following are considered non-compliant with this policy.

a. Failure to obtain a determination in writing from the HSPB or WRAIR IRB Chair/Designee as outlined in section 6 above, as to whether an activity is research involving human subjects, prior to initiating the activity.

b. Failure to notify the HSPB when an activity that began as “Not Research” evolves into research, or failure to notify the HSPB/WRAIR IRB when an activity that began as NHSR evolves into research involving human subjects. Other modifications that require HSPB notification include:

(1) A change in study objectives,

(2) A change in the roles/responsibilities of WRAIR investigators,

(3) A change in the source of samples/data,

(4) A change in funding, or

(5) Investigator access to information that could identify individual donors.

c. In response to a finding of non-compliance with this policy, the WRAIR IRB could recommend to the Commander, WRAIR, any of the following:

(1) Suspension or termination of the project,

(2) Destruction of data obtained prior to HSPB notification,

(3) Additional human subjects training for the study team, and/or

(4) Other sanctions (see WRAIR SOP UWZ-C-606, Non-Compliance Procedures).

10. Point of contact for this memorandum is Ms. Jody Ference, Director, Human Subjects Protection Branch (FCMR-UWS-HP) at Jody.L.Ference.civ@health.mil or 301-319-9940.