



DEPARTMENT OF THE ARMY  
WALTER REED ARMY INSTITUTE OF RESEARCH  
503 ROBERT GRANT AVENUE  
SILVER SPRING, MD 20910-7500

REPLY TO  
ATTENTION OF

MCMR-UWZ-C

5 March 2012

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: WRAIR Policy Letter 12-09, Determination that an Activity Is Research Involving Human Subjects

1. References.

a. 32 Code of Federal Regulations (CFR) 219, National Defense, Protection of Human Subjects

b. Department of Defense (DoD) Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research, dated 20 October 2011

c. 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, dated 18 April 1979

d. Army Regulation (AR) 70-25: Use of Volunteers as Subjects of Research, Headquarters, Department of the Army, dated 25 January 1990

e. U.S. Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP). OHRP Guidance on Research Involving Coded Private Information or Biologic Specimens, dated 16 October 2008

f. Department of the Army, U.S. Army Medical Research and Materiel Command (USAMRMC), Command Policy 2010-51, Ethical Use of Human Cadavers in USAMRMC Research, 8 November 2010

g. WRAIR Policy Letter 12-05, Submission of Protocols Involving Human Subjects, Human Specimens, and/or Human Data for Scientific and Ethical Review

2. History. This policy is being issued in accordance with WRAIR and MRMC requirements. This version of the policy supersedes WRAIR Policy Letter 08-03, and will remain in effect until amended or rescinded.

3. Purpose and Scope. This policy is intended to:

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

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b. Outline the general process within the Walter Reed Army Institute for Research (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 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).

#### 4. Definitions.

a. Research – Any activity which is a systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge (32 CFR 219.102(d)). The term "systematic investigation" is not further defined in 32 CFR 219. However, the Belmont Report states that research involving human subjects is:

(1) Part of a systematic investigation to test an hypothesis and permit conclusions to be drawn, usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective; and

(2) Intended to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).

b. Human Subject - a living individual about whom an investigator (whether professional or student) conducting research obtains:

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

(a) Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

(b) Interaction includes communication or interpersonal contact between investigator and subject.

(c) "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and the individual can reasonably expect will not be made public (for example, a medical record). Private information

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must be individually identifiable (i.e., the identity of the subject is or may be readily ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (32 CFR 219.102(f)).

c. Coded – Coded is defined in OHRP Guidance on Research Involving Coded Private Information or Biologic Specimens (dated 16 October 2008) as:

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

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

(3) Private information or specimens are considered to be individually identifiable when they can be linked to specific individuals through coding systems by any member of the research team or management of that research team.

d. Anonymized – For the purposes of this policy, “anonymized” refers to coded specimens or data, for which the key or link to decipher the code has been destroyed.

e. Anonymous - For the purposes of this policy, “anonymous” refers to specimens or data, for which no identifying private information was initially collected.

f. Official Tasker – An obligating document detailing a required activity, which originates from a Command-level, is routed through appropriate channels and receives official support from the WRAIR Commander.

5. Determination of the Applicability of 32 CFR 219. The determination that an activity is or is not “research involving human subjects” will be made solely by the Human Subjects Protection Branch (HSPB) or the Chair of the WRAIR Institutional Review Board (IRB). Investigators are required to contact the HSPB before initiating the proposed activity. See Submission Policy and 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. Procedure.

a. The Principal Investigator (PI) or WRAIR Point of Contact (POC) will submit a brief written description of the proposed activity to include an explanation of why it does or does not constitute “research involving human subjects” and applicable supporting documentation (e.g.

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Branch Director's memorandum, protocol, appropriate training, etc) to the HSPB mailbox [WRAIRHSPB@amedd.army.mil](mailto:WRAIRHSPB@amedd.army.mil).

b. Templates and guidance on preparing the submission may be obtained by contacting the HSPB at 301-319-9940, by visiting WRAIR's intranet (see WRAIR Submission Policy #12-05), or by visiting the HSPB website at [www.WRAIRHSPB.com](http://www.WRAIRHSPB.com).

c. The submission will be evaluated by the HSPB Director, IRB Chair, or designee for a determination:

(1) The activity is either "research" or "not research" in accordance with 32 CFR 219.102(d).

(2) If research, the activity is either "involving human subjects" or not, in accordance with 32 CFR 219.102(f).

d. If it is determined that an activity is "not research" (i.e. public health, clinical care, quality assurance), an email acknowledgment of the project (or a signed, written document) will be provided to the submitting investigator.

e. If it is determined that the activity is "research not involving human subjects" (NHSR), the HSPB will provide the investigator with a signed, written determination for the project. The PI (or WRAIR POC) is responsible for obtaining other applicable agreements (e.g. CRADA-MTAs, MOAs, import permits, etc) prior to work and/or shipment of any specimens or data. Please note: The HSPB may independently review the labeling of specimens and data to verify the NHSR determination, as well as, business agreements, as part of post-approval monitoring.

f. For NHSR projects, if WRAIR is the PI/Lead vs. a secondary collaborator, non-WRAIR institutional approvals/determinations will need to be in-hand prior to issuance of approvals/acknowledgments.

g. If the activity is determined to be research involving human subjects, a protocol and IRB review will be required. For submission guidance, please see the WRAIR Submission Policy 12-05. Once a complete submission is received by HSPB, the protocol will be forwarded to the WRAIR Office of the Science Director (WOSD), if applicable, for compliance with scientific review requirements (see Scientific Review Committee (SRC) SOP).

**Note:** 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.

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h. An activity that began as “not research” may change or evolve into research. Or, an activity that began as 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. As such, amendments to these projects must be submitted to the HSPB for an updated review determination to ensure any changes have not upgraded the risk level determination. This updated review determination will generally be in the form of an email acknowledgment, if the risk level remains unchanged.

7. Examples of Activities which require the HSPB to Determine whether (or not) they are Human Subjects Research.

a. Quality assurance. This refers to activities such as those carried out under 10 USC 1102 and Department of Defense (DoD) Directive 6025.13, Medical Quality Assurance in the Military Health System, dated 4 May 2004. 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 DoD Directive 5141.2, Director of Operational Test and Evaluation (DOT&E), 25 May 2000. 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. Research using private information (data) or specimens. Research that involves private information or specimens, which cannot be linked directly or indirectly (e.g. via a code link or key) to specific individuals requires a written determination from the HSPB that the activity is not research involving human subjects.

e. Research involving coded private information or specimens may be determined to not constitute human subjects research if investigator(s) cannot readily ascertain the identity of the individual(s) for one of the following reasons:

(1) 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 subjects are deceased; (There is a requirement for the WRAIR IRB/HSPB to review and file this document);

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

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

**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 by the IRB, which could allow for a department staff member to maintain the key (on a case-by-case basis) with specific safeguards in place.

f. 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. (i.e., they are not transformed.)

g. Research with cadavers. There are additional oversight requirements for these activities, per the U.S. Army Medical Research and Materiel Command (USAMRMC) Policy 2010-51.

**Note:** 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 through MRMC detailing WRAIR's roles and responsibilities.

h. These activities may still require corresponding business agreements. Please seek guidance from the Office of Research Technology Applications (ORTA).

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

a. Pooled specimens. Pooled products, such as pooled sera, plasma, cells, or coagulation factors may be used in research without a submission to the HSPB (32 CFR 219 does not apply), as no code or personal identifier would exist for such products.

b. Command-Directed non-research activities. These activities must not qualify as research per 32 CFR 219. 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.

c. Research involving autopsy material and/or biological specimens or private

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information from now deceased individuals. 32 CFR 219 does not apply to these activities, as they do not involve living human beings. However, there may be additional oversight requirements for certain activities (i.e. use of cadavers), per the U.S. Army Medical Research and Materiel Command (USAMRMC) (See 7.f. above).

d. Research involving established cell lines (e.g. 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.)

e. Commercially available biological materials. The use of commercially purchased human biological materials unaccompanied by identifiable data (i.e. 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.

f. 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 (see 7.d.).

g. Provision of samples/data: Sending samples and data to a 3rd party is not a research activity, unless the WRAIR will be receiving information in return. Original intent and usage allowances should be considered, as well as, original collaborator permissions. Business agreements and local regulatory approvals of receiving institutions are required.

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

a. Failure to get a determination in writing from the HSPB (or WRAIR IRB Chair) as outlined in 7. 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 for research purposes” 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, or

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

c. In response to a non-compliance finding (if a project would have been considered “research”), 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 other sanctions.

10. Points Of Contact. The points of contact for this policy are the Chair, WRAIR IRB, and the Director, HSPB, at (301) 319-9940.

**Signature on File**

RALPH L. ERICKSON  
COL, MC  
Commanding

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