



REPLY TO
ATTENTION OF

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

MCMR-UWZ-C

06 March 2012

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: WRAIR Policy Letter 12-12, Human Subjects Research Protocol Closure Policy

1. References.

- a. Department of Defense (DoD) Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research, 20 October 2011
- b. 32 Code of Federal Regulation (CFR) 219, Protection of Human Subjects, 1 July 1999
- c. 21 CFR 50, Protection of Human Subjects and 21 CFR 56, Institutional Review Boards, 1 April 2003
- d. 21 CFR 312, Investigational New Drug Applications
- e. 21 CFR 812, Investigational Device Exemptions
- f. Federal Food, Drug, and Cosmetic Act, Chapter V, Sections 505 and 520
- g. Guideline for Industry, Structure and Content of Clinical Study Reports, ICH3, July 1996
- h. Army Regulation 70-25, Use of Volunteers as Subjects of Research, 25 January 1990
- i. Message, ALARACT 031/2008, Army Human Subjects Protection Requirements, DTG 141557Z, February 2008.
- j. Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 1979.
- k. Human Research Protection Plan (HRPP), Walter Reed Army Institute of Research, July 2008.
- l. United States Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO), Human Subjects Research Review Board (HSRRB), Policies and Procedures Manual, Version 1, dated 14 March 2005

2. History. This policy is being issued in accordance with WRAIR & USAMRMC requirements. This version of this policy will remain in effect until amended or rescinded.

This Policy Letter supersedes WRAIR Policy Letter 10-02, dated 24 May 2010.

3. Purpose. This policy defines timelines and criteria for closure of human subjects research protocols by the Walter Reed Army Institute of Research (WRAIR), Institutional Review Board (IRB) in order to maintain both scientific integrity of the research process and regulatory compliance with regards to human subjects protection.

4. Definitions.

a. Clinical Investigation. Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration (FDA) under section 505(i) or 520(g) of the Act, or is not subject to requirements for prior submission to the FDA under these sections of the Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

b. Clinical Study Report. An "integrated" full report of an individual study of any therapeutic, prophylactic, or diagnostic agent, or investigational device, conducted in patients, written by the study sponsor.

c. Closeout Report. A brief summary of a human subjects research study reported to a USAMRMC Institutional Review Board, which indicates that all work on the research study has been completed and the study may be closed. The reports are usually no more than 3-10 pages in length.

d. CONUS. Continental United States

e. Human Subjects Protection Branch (HSPB). The administrative support for the WRAIR IRB.

f. Engaged in Human Subjects Research. An institution is engaged in human subjects research if its employees (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes.

g. Extramural Research. USAMRMC-managed research that is conducted at non-USAMRMC sites by non-USAMRMC investigators.

h. Final Study Report. A report written by the study investigator for submission to the study Sponsor that summarizes the results of a clinical investigation at a study site once the site's participation in the clinical investigation is complete.

i. Human Research Protection Program (HRPP). The institutional program established to outline responsibilities and procedures for protecting the rights and safeguarding the welfare of human subjects who participate in research conducted or supported by that institution.

j. Institutional Official (IO). Individual ultimately responsible for implementation of the DoD assurances of compliance for the protection of human research subjects and the associated human research protection program at an institution engaged in human subjects research.

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Within the USAMRMC, the Commander of the institution/organization engaged in research is the institutional official.

k. Intramural Research. Research that is conducted within USAMRMC facilities and/or is conducted or funded by USAMRMC personnel.

l. OCONUS. Outside Contiguous United States

m. Principal Investigator (PI). Individual ultimately responsible and accountable for designing, conducting, and compliance with a research protocol. The PI is the leader of the research team; and assumes full responsibility for the treatment and evaluation of the research subjects and the integrity of the research data.

n. Research Involving Human Subjects. Any research study that involves human subjects, identifiable human data, or identifiable human anatomical substances.

o. Sponsor. An organization which takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. The United States Army Medical and Materiel Development Activity (USAMMDA) serves as the sponsor and Investigational New Drug (IND) application holder when investigators within USMRMC initiate the development of a new experimental product and conduct clinical investigations with the new experimental product. There are no sponsor-investigators in the USMRMC.

p. WRAIR Institutional Review Board (IRB). The ethical review committee for research involving human subjects at WRAIR, its detachments, or when WRAIR funding, facilities or personnel are involved in any way (investigator, consultant, collaborator, etc.) This includes protocols for which recruitment of subjects is being performed at WRAIR.

q. WRAIR Point of Contact (POC). Individual responsible for the oversight of the work being conducted on a human subjects research protocol at WRAIR or a WRAIR detachment. For research studies involving non-WRAIR PIs, the WRAIR POC is responsible for ensuring that the work being conducted under the WRAIR HRPP meets all the appropriate regulatory requirements. They ensure that all of the appropriate regulatory documentation is submitted to the WRAIR DHSP and WRAIR IRB as appropriate.

5. Background. Prior to the issuance of the 1st version of this policy, USAMRMC rescinded Command Policy 98-02, which required the closure of intramural protocols within a five-year time frame. Individual USAMRMC institutions are therefore required to initiate their own closure policies. WRAIR will maintain the five-year time frame for intramural protocols as originally stated in the USAMRMC Command Policy with a few changes regarding extensions and exceptions.

This Policy Letter supersedes WRAIR Policy Letter 10-02, dated 24 May 2010.

Protocol closure criteria are established by the Office of Human Research Protections (OHRP), Human Health Services (HHS), and Human Research Protections Office (HRPO) policies and procedures, which state protocols must remain open when research activities are ongoing. Protocols may be closed only when all study activities, such as enrollment and follow up of subjects, and data analyses, have been completed. According to the USAMRMC ORP HRPO Policies and Procedures Manual (on page 52-53 section IV.H.3.c, "Protocol Completion"), "A study is defined as completed if it is closed voluntarily by the Principal Investigator (PI) because: (i) the study is closed to further enrollment of subjects; (ii) the research team has completed all of the specific aims including data collection and analyses as identified in the research protocol; and (iii) the PI has submitted the final report(s). Because no activity whatsoever will take place on this study in the future, it is thereby voluntarily closed by the PI." The preparation of manuscripts and clinical study reports are exceptions to this rule. Manuscript and/or clinical study report preparations are not research activities, unless re-analysis or new analyses of the data are required to be performed by the study site, therefore the study can be closed while manuscripts and clinical study reports are being written and submitted for review unless data analysis is ongoing at the study site.

6. Applicability and Scope. This policy applies to all WRAIR and WRAIR detachments (CONUS and OCONUS) intramural human subjects research protocols (including exempt, minimal risk, greater than minimal risk) and which the WRAIR is responsible for overseeing under their HRPP. This policy does not apply to extramural human subjects research protocols.

7. Policy. All WRAIR intramural protocols, to include exempt, minimal risk, and greater than minimal risk studies, will be closed five years from the date of final approval (by the WRAIR IRB) unless otherwise requested and approved during the initial protocol review or unless the PI is granted an extension. Studies may be given less than 5 years, based upon the parameters set by the protocol.

a. At the time of the initial protocol review, exceptions to the five-year policy may be considered based on the type of study being conducted. The study team may request a longer pre-determined study time frame with strong justification provided. This request should be submitted as part of the submission memorandum to the Human Subjects Protection Branch (HSPB) for review and consideration by the WRAIR IRB Chair or the full WRAIR IRB, as appropriate. The approved protocol closure date will be noted in the initial approval memorandums.

b. If data analysis for an ongoing human subjects research study has not been completed by the pre-determined closeout date established during the initial protocol review, investigators may request a one-time extension by submitting an extension request stating the length of time needed (from 6 months to 3 years), a strong justification for the extension, and a summary of the work remaining. A second extension of these human subjects research studies may be considered under extenuating circumstances, however, strong justification must be provided. Exceptions to this extension policy are protocols such as repository, cohort development, epidemiology, or those, which by their very nature may require extensions up to 5 years each. At the discretion of the WRAIR IRB Chair or WRAIR IRB, as appropriate, up to two extensions with a strong justification will be considered.

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c. All protocol extensions may require both a scientific review and a human subjects protection review (conducted by the HSPB, WRAIR IRB Chair, and/or the fully convened WRAIR IRB) as additional protocol modifications may be required to update regulatory reporting requirements. Investigators should plan to submit extension requests at least 30 days prior to the pre-determined protocol closure date to allow time for review and approval, and to avoid interruptions in work. If a closeout report or extension request has not been submitted by the pre-determined protocol closure date, then the protocol will be involuntarily closed by the WRAIR Institutional Official within 30 days following the protocol expiration. This ensures that the IO is informed of PIs who are not adhering to the WRAIR policies and approved protocol deadlines. Submission of a closeout report is still a mandatory requirement. No work is to be conducted once the pre-determined protocol closure date is met and the protocol has expired. Once a protocol is officially closed, it can only be formally reopened as a new protocol.

d. For all exempt, minimal risk, and greater than minimal risk human subjects research studies (including both intramural and extramural studies) reviewed and approved by the WRAIR IRB, it is required that a closeout report be submitted by the WRAIR POC or WRAIR PI once all study activities have been completed at WRAIR.

8. Point of contact. The Point of Contact for this policy is the Director, Human Subjects Protection Branch, at (301) 319-9940 or wrairhspb@amedd.army.mil.

Signature on File

RALPH L. ERICKSON
COL, MC
Commanding

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