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

FCMR-UWZ (1200B) 10 April 2024

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

SUBJECT: WRAIR Policy #30, Human Subjects Research Protocol Closure

1. References.

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

b. Food and Drugs, 21 C.F.R. §§ 50.1-50.56 and §§ 56.101-56.124 (2018).

c. Food and Drugs, 21 C.F.R. §§ 312.1-312.320, (2018).

d. Food and Drugs, 21 C.F.R. §§ 812.1-812.150, (2108).

e. Federal Food, Drug, and Cosmetic Act, Chapter V, Sections 505 and 52, 30 September 2023.

f. Structure and Content of Clinical Study Reports, E3, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), July 1996.

g. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry), dtd March 2018, exp. 30 September 2026.

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

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

---

*This supersedes WRAIR Policy #30, dated 27 January 2022.

k. USAMRDC Policy 12 (Requirements for Initial and Ongoing Education and Training in the Protection of Human Subjects in Research).

l. USAMRDC Policy 16 (Investigating, Managing, and Reporting Noncompliance with Human Subjects Research Regulatory Requirements).

m. USAMRDC Policy 17 (Event Reporting Requirements for Human Subjects Research Conducted by the USAMRDC).

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

o. USAMRDC Policy 26 (Medical Care for Research-Related Injury in Human Research Conducted by the USAMRDC).

p. USAMRDC Policy 45 (Army Records Information Management System Record Titles for Army Regulation 70-25, Use of Human Subjects of Research).

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

r. Memorandum, UWS-HP-618, FCMR-UWS-HP (WRAIR Standard Operating Procedure for Continuing Review and Continuation Determination).

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 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. The purpose of this policy is to define timelines and criteria for closure of exempt and non-exempt human subjects research protocols (minimal risk, and greater than minimal risk) by the WRAIR IRB to maintain both scientific integrity of the research process and regulatory compliance with regards to human subjects protection. In addition, this policy defines the reporting requirements for “Public Health Activities (PHA)”, “not research (NR)” and “research not involving human subjects (NHSR)” projects after activities are completed.

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. The term does not include experiments that are subject to the provisions of 21 C.F.R. § 58, regarding nonclinical laboratory studies.

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

c. Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

d. Closeout Report: A brief summary of a human subjects research study reported to an IRB, which indicates that all work on the research study has been completed and the study may be closed.

e. Completion Notification: Email or memorandum transmitted via email notifying the Human Subjects Protection Branch (HSPB) that a "not research" or "research not involving human subjects" project has been completed and that no further work with data or specimens will occur without a new protocol submission.

f. Engaged in Human Subjects Research: An institution is engaged in research involving human subjects if its employee(s) (i) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens for research purposes; or (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens for research purposes.

g. Final Study Report: A report signed by the study Principal Investigator (PI), site PI, or designee, for submission to the study Sponsor, US Food and Drug Administration (FDA), or other applicable regulatory authorities, that summarizes the results of the human subjects research or clinical investigation at a study site once the site's participation in the research or clinical investigation is complete.

h. Human Research Protection Program (HRPP): An integrated institution-wide program coordinated by the Human Subjects Protection Branch (HSPB) with the main purpose of ensuring all of WRAIR's activities related to human subjects research are conducted in accordance with regulatory requirements and ethical principles as set forth in the Belmont Report. Major components of the HRPP include the Institutional Review Board (IRB), research review groups [the Research Programs Office (RPO), Scientific Review Committee (SRC), Institutional Biosafety Committee (IBC), WRAIR Safety

Office, USAMRDC Human Research Protections Office (HRPO)], assurances, regulations, policies, standard operating procedures (SOPs), investigators, sponsors, WRAIR Centers and Directorates, USAMRDC Headquarters, etc.

i. Human Subjects Protection Branch (HSPB): The administrative support team for the WRAIR IRB and the WRAIR HRPP (i.e., IRB Support Staff, Human Subjects Protection Scientists, IRB Administrators, Human Protection Administrators, Exempt Determination Officials).

j. Institutional Official (IO): Individual ultimately responsible for the implementation of the U.S. Department of Health and Human Services (DHHS) Federal wide Assurance and the DOD Assurance of Compliance for the Protection of Human Research Subjects and the associated HRPP at an institution engaged in research involving human subjects. Within the USAMRDC, the Commander of the institution/organization engaged in research is the IO.

k. Principal Investigator (PI): The individual who is responsible and accountable for conducting a research study. This individual will have the appropriate scientific and ethics training and experience to assume full responsibility and accountability for the scientific integrity of the research data and results. The PI is the individual responsible and accountable for designing, conducting, and monitoring the research study, and has access to the data. For studies involving human research subjects, the PI, as the leader of the research study team, assumes full responsibility for the medical care and evaluation of subjects, either directly or indirectly (designee of a healthcare provider). The PI also is responsible for protecting the rights and welfare of human subjects and is responsible for carrying out sound ethical research consistent with research plans in a protocol approved by a properly-constituted IRB. The PI may formally delegate roles and responsibilities to other members of the research study team, as appropriate, but retains full responsibility for the conduct of all study activities.

(1) FDA Definition: Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(2) ICH E6 Definition: Investigator means a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Note: The above definition is not necessarily the same as that of a PI listed on a grant or research award, which may include other responsibilities not involving human subjects research.

l. Research: A systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge (32 C.F.R. § 219.102d).

m. 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.

n. Sponsor: An individual, company, institution or organization that takes responsibility for the initiation, management, and/or financing of clinical research (ICH E6). 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 investigate that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. The USAMRDC Principal Assistant for Acquisition (PAA) serves as the Sponsor's Representative when programs within USAMRDC initiate the development of a new experimental product and conduct clinical investigations with the new experimental product. There are no sponsor-investigators in the USAMRDC.

o. WRAIR IRB: The committee that has been formally designated to review, approve, and monitor biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the research subjects at WRAIR, its Directorates, 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. Selection for the board is in accordance with Federal guidelines outlined in 21 C.F.R. § 56.107 and 32 C.F.R. § 219.

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 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 or administrative capacity.

5. Background.

a. USAMRDC rescinded the Command Policy 98-02, which required intramural protocols to close within a five-year time frame. Individual USAMRDC institutions are therefore required to initiate their own closure policies.

b. WRAIR will maintain the five-year time frame for intramural protocols as originally stated in the USAMRDC Command Policy with a few changes regarding extensions and exceptions.

c. Protocol closure criteria are established by the Office of Human Research Protections (OHRP), DHHS, and USAMRDC Office of Human and Animal Research Oversight (OHARO) policies and procedures, which state protocols must remain open when research activities are ongoing. Protocols may be closed only when all study activities, including subject recruitment and all subject interactions (including long term follow-up), planned experiments, and analyses or manipulations of research materials (data/specimens), have been completed.

d. When WRAIR participates in multi-site research studies, once study enrollment is closed and interventions with subjects are complete, a closeout report will be submitted to the HSPB only after the study sponsor has closed the WRAIR Center or Directorate as a study site. This includes: the sponsor's close-out visit is complete, and all outstanding issues have been addressed; access to identifiable biospecimens, data and records (e.g., source documentation) is no longer needed by the WRAIR study team, sponsor or sponsor representatives; and all contractual and budgetary issues are complete (e.g., payments to subjects; billing to sponsor or third party insurance).

e. 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 analyses are ongoing at the study site.

6. Applicability and Scope. This policy applies to all WRAIR and WRAIR Directorates exempt and non-exempt (minimal risk and greater than minimal risk) human subjects research protocols which WRAIR is responsible for overseeing under its HRPP. Projects deemed "not research (NR)," "research not involving human subjects" (NHSR) and PHA have closeout requirements as well, but this is achieved via an email close out notification. The level and amount of detail required in close out notifications are dependent upon the type of project.

7. Policy.

a. All human subjects research protocols (including exempt, minimal risk and greater than minimal risk) which the WRAIR is responsible for overseeing under its HRPP, will be closed **five years** from the date of final approval by the WRAIR IRB (or Exemption Determination Official (EDO)), unless otherwise requested and approved during the initial protocol review or unless the PI is granted an extension. Where

applicable, timing of protocol closure should match the corresponding business agreement or funding timelines.

b. 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 HSPB for review and consideration by the WRAIR IRB Chair IRB Chair Designee or the EDO, as appropriate. The approved protocol closure date will be noted in the initial approval memoranda, as well as other protocol actions approval memoranda (e.g., amendments, continuing reviews, etc.).

c. If data/specimen 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. At the discretion of the WRAIR IRB, WRAIR IRB Chair, the IRB Chair Designee, or EDO, as appropriate, a second extension of these human subjects research studies may be considered under extenuating circumstances; however, strong justification must be provided. Protocols such as repository, cohort development, epidemiology, or those, which by their very nature may require longer extensions (up to 5 years each) are an exception to the extension process above.

d. All protocol extensions may require both a scientific review and a human subjects review (conducted by the HSPB, WRAIR IRB Chair, the fully convened WRAIR IRB, and/or the EDO) as additional protocol modifications may be required to update regulatory reporting requirements. Investigators should plan to submit extension requests at least 30 days (for studies conducted within the continental US) or 90 days (for studies conducted outside the continental US) prior to the pre-determined protocol closure date to allow time for review and approval, and to avoid interruptions in work.

e. If a closeout report or extension request has not been submitted and approved by the pre-determined protocol closure date, then the protocol will be involuntarily expired by the WRAIR IO. The protocol will be involuntarily closed within 30 days following the protocol expiration if an extension is not approved, or a close out report provided before this time. 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 a mandatory requirement for all human subjects research protocols. No work is to be conducted once the protocol closure date is met or if the protocol has expired. Once a protocol is officially closed, it can only be formally reopened after it has undergone the initial review and approval process as a new protocol.

f. For all exempt, minimal risk, and greater than minimal risk human subjects research studies reviewed and approved by the WRAIR IRB, it is required that a closeout report be submitted by the WRAIR PI or WRAIR POC once all study activities have been completed at WRAIR. Refer to WRAIR SOP UWS-HP-637 for close out report templates.

g. For human subjects research studies where WRAIR has deferred IRB review to another institution, the closure date will be determined by the institution providing IRB review. However, the WRAIR POC is required to provide progress reports to HSPB as to the estimated date of closure if beyond five years or the timeline stated in the protocol.

h. Requirements for PHA, NR and NHSR projects. The WRAIR PI or WRAIR POC must submit a completion notification via email notifying HSPB when the project has been completed. At a minimum this notification should contain the protocol title, WRAIR number, PI name, date completed, disposition of samples/data, and any known future plans. PHA notifications should also contain a summary of information provided to the requesting Public Health Authority and report upon any modifications to policy or guidance because of the PHA. Upon receipt of the completion notification, the HSPB will issue an acknowledgement email or memorandum for the investigator's files. Refer to WRAIR SOP UWS-HP-637 for template notifications.

i. There are instances where a protocol has incurred amendments that have significantly altered the intent of the study over time or no longer reflect current regulatory requirements. In these circumstances, the WRAIR IRB (exempt, minimal risk, greater than minimal risk) and HSPB (for NR/NHSR) can request a replacement submission to better synchronize amendments that have occurred into a new, cleaner protocol.

j. Once a protocol or project has been closed at the WRAIR, the WRAIR PI or the WRAIR POC is responsible for notifying all Associate Investigators, collaborators, etc., that no further work can occur until a new protocol has been submitted, reviewed and approved. The WRAIR does not re-open closed protocols.

8. 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.