SOP Title	**POST APPROVAL COMPLIANCE MONITORING FOR HUMAN SUBJECTS RESEARCH**	SOP No.	UWS-HP-633
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1. Purpose and Applicability

This Standard Operating Procedure (SOP) sets forth a mechanism for routine post approval compliance monitoring (PACM) of human subjects research conducted by the Walter Reed Army Institute of Research (WRAIR). Post Approval Compliance Monitoring is a required function of a Human Research Protection Program (HRPP) as per DODI 3216.02 (29 June 2022 version). This monitoring serves as a tool to assess whether human subjects research is being conducted in compliance with governing federal regulations WRAIR policies, Institutional Review Board (IRB) approved protocol, and/or other applicable regulations. The results of the review provide an opportunity to identify and develop focused training programs for investigators, their research staff, Human Subjects Protection (HSPB) staff and the IRB members, as well as, provide dialogue with Investigators and research staff.

Scope: Studies scheduled for monitoring will be representative of WRAIR's research portfolio and will include exempt research, minimal risk & greater than minimal risk research, as well as, not research (QA, Public Health), and non-human subjects research (NHSR). Studies will be selected based on risk assessment for routine PACM. Studies may also be selected for Directed PACM by WRAIR IRB, HSPB Director or Designee.

Studies wherein WRAIR has deferred IRB review to another institution can be selected for Post Approval Compliance Monitoring pursuant to the IRB Reliance Agreement.

2. Responsibilities

This SOP applies to the HSPB Director/IRB Administrative Director and Staff, the IRB Chair/Designee, IRB members, and the Institutional Official (IO).

a. The HSPB staff (generally Post Approval Compliance Monitors) conducts monitoring on behalf of the Director, HSPB, IRB, and/or IO, writes monitoring reports and keeps the HSPB Director informed of the monitoring activities. In addition, the HSPB staff, provides administrative support to the IRB in fulfilling their responsibilities under this SOP (hereafter, referred to as 'monitor(s)' for the purposes of this SOP).

b. The IRB Chair (or Designee) and IRB members participating in the compliance monitoring visit assist the monitor(s) by reviewing the monitoring reports and making recommendations for quality improvement, as well as, identifying/addressing non-compliance, per the Non-Compliance Procedures SOP (UWS-HP-606).

c. The IO and the IRB are informed if non-compliance is discovered during routine monitoring, per the Non-Compliance Procedures SOP (UWS-HP-606).

d. The IO is responsible for final adjudication of any findings. He/she may take a more strict tact than prescribed by the IRB, but cannot reduce any requirements or restrictions imposed by the IRB.

3. **Materials and Equipment**

Not Applicable

4. **Investigator Guidance**

The Principal Investigator (PI)/WRAIR Point of Contact (POC) is expected to:

a. Respond to all requests for information from the monitor(s) and/or IRB (if applicable) in a timely manner, and

b. Comply with any determinations made by the reviewing IRB and the IO regarding the research or appeal the determination per the Appeal of IRB Decision SOP (UWS-HP-612).

5. **Background**

a. Routine monitoring is conducted by HSPB monitor(s). At the request of the IRB Chair/IRB Administrative Director/IO, IRB members may also participate in the routine monitoring of human subjects research. Additionally, at the request of the U.S. Army Medical Research and Development Command (USAMRDC), Office of Human and Animal Research Oversight (OHARO), Office of Human Research Oversight (OHRO), monitors from USAMRDC may also participate. Routine monitoring should be a non-punitive review that gives the PI/WRAIR POC and research staff feedback on the human subjects protection conduct of their protocol and provide an opportunity for questions and answers.

b. The monitor(s) may review the IRB's records to determine accuracy and consistency with the investigator's research records and to verify that the investigator made no material changes to the protocol without IRB approval and/or Commander Approval Authorization. The findings of the routine monitoring are shared with the PI/WRAIR POC, research staff and IRB. If the

findings reveal non-compliance with the human subjects protections program, actions per Non-Compliance Procedures SOP UWS-HP-606 will be initiated.

c. Directed monitoring is conducted by HSPB monitor(s) upon the request of WRAIR IRB, IO, HSPB director, HSPB designee due to unusual circumstances, potential significant risks to subjects, routine failure on the part of an investigator to comply with federal and/or institutional requirements, or allegations/concerns about the conduct of the study.

i. Directed monitoring may range from full PACM review to review of specific items pertinent to the directed nature of the monitoring.

ii. Assessment of the depth of the directed PACM is conducted by monitor(s) and authorized by the HSPB Director.

6. **Actions**

a. **Prior to PACM Visit**

1) Study Selection: Using the risk assessment tool, (Appendix D) and/or a suggestion from HSPB, monitor(s) may select a protocol for review based on a variety of criteria including, but not limited to: IRB review, study funding source, off-site research, protocol event types, specific research categories,

WRAIR department, PI, studies currently approved and active for one year, or number of subjects currently enrolled in a protocol.

a) All studies affiliated with WRAIR and/or for which the WRAIR IRB is the IRB of Record, may be monitored a minimum of one time during the duration of the trial.

b) Closed studies can also be chosen for review within 3 years of their close out report.

2) Approval for Monitoring: Approval for monitoring is granted by the HSPB Director, IRB Chair, or IO.

3) Scheduling PACM Visit: Once it is determined which protocol(s) is/are to be monitored, a monitor notifies the PI in writing, via email, of the upcoming routine review.

The time frame of advance notice of a site review is a minimum of two weeks with added flexibility for the PI's availability.

Note: Due to extenuating circumstances that limit on-site monitoring (e.g. global pandemics), remote PACM visits may be conducted virtually using internet-based tools. During such monitoring visits, the monitor(s) will provide an explanation of the tools available for file-sharing and virtual meetings, i.e. DoD Safe Secure, Microsoft Teams, or the applicable software used by WRAIR/HSPB at the time of the monitoring visit. Study teams will be given notice to establish secure and encrypted file transfer in advance of the scheduled monitoring visit. Additionally, when a review is to be conducted at a distant site location (i.e., U.S. Army Medical Research Directorate-Africa, U.S. Army Medical Research Directorate-Georgia, Armed Forces Research Institute of Medical Sciences) the visit may also be conducted via remote/virtual review. If travel for a visit occurs, preparation and travel time, as well as staffing needs will be considered when establishing review dates.

The date upon which the study team begins to send documents relevant to monitoring to the study team is entered in the HSPB database as the start date of monitoring.

4) Visit Preparation: Prior to the monitoring visit, the monitors may view the initial IRB review meeting minutes (if applicable) and all subsequent lifecycle actions taken by the IRB, IRB records, the HSPB database and

communication with the study's designated Human Subjects Protection Scientist POC, to become familiar with the protocol(s) and to identify any potential issues to address during the monitoring process. Monitors notify HSPB POC of PACM visit scheduling and request any additional information as needed for specific studies.

a) Internal File Audit (IFA): In preparation for a PACM event, monitor(s) may conduct an internal audit of HSPB records including but not limited to HSPB database entry, initial study review, amendment approval and authorizations, continuing review report and approval, SAE/UAP actions, and relevant correspondence.

b) IFA findings and recommended actions are communicated to the HSPB Director or Designee and HSPB POC.

b. **PACM Visit**

1) Entrance Interview:

a) The entrance interview precedes the review of the PI's/WRAIR POC's research records/on-going study activities. The monitors may use this time to explain the goals of the monitoring visit and may provide a file review list.

b) The PI/POC/research staff may take this opportunity to explain what the protocol entails and answer any preliminary questions arising from the review of the WRAIR IRB protocol records.

c) This entrance interview includes and is not limited to email communication, e-meeting, a scheduled teleconference, or a scheduled video conference with the PI/study team.

2) Document Review:

a) The records, activities and items to be reviewed at the site may consist of, but are not limited to, the following:
- Protocol Binder/Regulatory Documentation - noting whether the records retained meet Federal, International Conference on Harmonisation, Good Clinical Practices, Good Manufacturing Practices (as applicable), Institution and IRB requirements and guidelines;
- IRB Documentation - comparing the PI/WRAIR POC records with the IRB records. Review of IRB documentation affords the opportunity to

determine whether the PI/POC made material changes prior to WRAIR IRB approval and Commander Approval Authorization;
- Consent Forms - when applicable, examining both individual and broad consent forms used to enroll the subjects to ensure that the subjects signed the appropriate consent form for their respective study and that the forms were properly completed, signed and dated;
- Case Report Forms (CRFs) - when applicable, determining if the subjects met all the inclusion criteria and none of the exclusion criteria for their respective study, the PI/research staff recorded and documented items properly, and whether a record serves as both a CRF and a source document;
- Source Documents/Medical Records - when applicable, reviewing source documents/medical records for clinical trials to verify the information in the CRFs, including storage and security, and that a copy of the signed consent form has been provided to the subject(s);
- Electronic and (scanned) hard copy study data to verify consistency with CRFs, source documents and approved protocol;
- Sponsor monitoring reports and/or follow-up letters, if applicable;
- Study Logs – when applicable, drug accountability logs, specimen storage logs, shipping logs, delegation of authority logs, signature/initial logs, enrollment logs, etc., will be reviewed;
- For on-site visits, observation of the consenting process and other study procedures, as well as direct contact with individual subjects, when feasible.

For assistance/clarification during the review, the monitors may contact the PI/WRAIR POC directly or, if applicable, inquire with the PI's research staff.

The date of receipt of all documents relevant to monitoring from the study team is entered in the HSPB database as the end date of monitoring.

Exit Interview: The monitor(s) conducts an exit interview with the PI/WRAIR POC and/or the PI's/WRAIR POC's Department Chief/Branch or Center Director/Directorate Director, as appropriate. At the PI's/WRAIR POC's discretion, select research staff may also attend.

b) The monitor(s) will conduct the exit interview after the completion of the review of the PI's records/study activities and may ask for clarification regarding the protocol or research procedures at that time. The Exit interview includes and is not limited to in-person discussion, email communication, e-meeting, a scheduled Teleconference, or a scheduled video conference with the PI/study team.

c) The monitor(s) will provide the investigator and/or Branch/Center/Directorate Director with a verbal summary of the findings and explain the remaining procedures for conclusion of the review. A hard copy of the Query and Clarification form (Appendix C) will also be provided.

d) The PI will be afforded the opportunity to clarify findings or correct inaccuracies at this time.

e) If identified as necessary during the Exit Interview, a follow-up meeting will be scheduled to close remaining/unclosed findings, queries and corrective action plans, as needed.

c. **Post PACM Visit:**

1) Monitoring Report: After the exit interview, the monitor(s) prepare a Monitoring Report (Appendix A) outlining the findings of the review pertinent to the PI/POC records, on-site observations, and interviews with the investigator and research personnel.

a) Monitors are authorized an opportunity to review and edit the report prior to finalization, as applicable.

b) As a means of maintaining confidentiality, the monitor(s) do not record subjects' protected health information in the review findings. The monitors are expected to complete their report within 10 business days of the final date when all requested files have been received from the site. If the files requested have not been received within a reasonable timeframe, following a suspense time of 2 business days, the submission window will be closed and any missing documents will be identified in the final report.

2) Report Review: The HSPB Director/Designee will review the draft Monitoring Report prior to it being sent to the PI. Any edits requested by the HSPB Director/Designee, will be incorporated within a maximum of 5 business days unless otherwise discussed.

3) Report and Response: Once the Monitoring Report is complete, the monitor sends it to the PI.

a) The results may or may not require a response from the PI. The monitors determine the date for any response on a case-by-case basis.

b) When a PI's response to the Monitoring Report is required, the response is reviewed by the monitor(s) to ensure all requested items have been addressed. The response from the PI is captured on the Query and Clarification Form (Appendix C) and filed with the routine monitoring report on the HSPB Post Approval Compliance Monitoring folder.

c) Additionally, the Routine Monitoring Report is provided to the HSPB Director and IRB Chair. The IRB Chair may provide the report to the full IRB, as deemed necessary. Substantive rebuttals may be referred by the IRB Chair to the full IRB for resolution.

4) Non-Compliance and Communication with IRB: When non-compliance is identified, a brief summary is reported to the IRB Chair. The IRB Chair also reviews the complete report and PI's/POC's response.

a) A determination is made as to whether further information (via a directed monitoring visit) is needed, or to forward the report and response for additional review or acknowledgement by the fully convened IRB.

b) If appropriate, the HSPB schedules a review of the PI's response with the full IRB at the next available IRB meeting. The IRB Chair or HSPB Director notifies the PI of this action. (Non-Compliance Procedures SOP UWS-HP-606 will be initiated.)

5) Database Entry: In the HSPB database, the monitor updates the dates of the monitoring visit.

6) Document Storage & Retention: Documents collected for review are stored on the limited access HSPB network drive in the Post Approval Compliance Monitoring folder. All identifiable documents received in the process of monitoring either remotely or in-person, are destroyed within 30 calendar days of completion of the report.

7) For any findings requiring review by the full IRB---refer to Standard Operating procedure UWS-HP-610, IRB Voting Requirements.

Electronic copies of all correspondence and reports are kept in a central file, within the HSPB for all routine monitoring visits conducted by HSPB, as well as the protocol e-files on the HSPB-access only shared drive.

Electronic copies of query sheets and worksheets (Appendices A, C, D & E) may be destroyed after the final response to the Monitoring Report has been received (if applicable).

5. References

Reference Number or Authors	Document Title
AR 40-68	Clinical Quality Management, 22 May 2009. Armypubs.army.mil
AR 70-25	Use of Volunteers as Subjects of Research, 25 January 1990
DODI 3216.02	Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and Supported Research
USAMRDC Policy 16	Investigating, Managing, and Reporting Noncompliance with Human Subjects Research Regulatory Requirements
USAMRDC Policy 17	Event Reporting Requirements for Human Subjects Research Conducted by the USAMRDC
WRAIR IRB Charter, Version 6	Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) Charter, Version 7, dated 20 December 2012
WRAIR HRPP	Walter Reed Army Institute of Research (WRAIR) Human Research Protections Program (HRPP), Version dated 23 January 2023
ICH-GCP-E6(R2)	Good Clinical Practice: Integrated Addendum to ICH E6(R1)
OHRP Guidelines	IRB Written Procedures: Guidance for Institutions and IRBs (2018) https://www.hhs.gov/ohrp/regulations-and-policy/guidance/institutional-issues/institutional-review-board-written-procedures/index.htm

Titles 21, 32 and 45	Code of Federal Regulations
Amdur, R. J. and Bankert, E. A.	Institutional Review Board Member Handbook (4th Edition), Boston: Jones and Bartlett Publishers, 2022
SOP UWS-HP-606	Non-Compliance Procedures
SOP UWS-HP-612	Appeal of IRB Decisions

7. **Appendices and Attachments**

Appendix or Attachment Number	Title
UWS-HP-633-A Appendix A	Post Approval Compliance Monitoring Report Template
UWS-HP-633-A Appendix B	Worksheet for Documenting Monitoring events in HSPB Database
UWS-HP-633-A Appendix C	Query and Clarification Form
UWS-HP-633-A Appendix D	Risk Assessment Tool

7. **Document Revision History**

Version Number	Brief Description of Changes	Effective Date
.00	New	15 October 2008
.01	Biennial Review; updated for consistency with current policies/procedures	06 April 2011
.02	Review and revisions to incorporate updated guidance, policies and regulations	17 March 2023