SOP Title **NON-COMPLIANCE PROCEDURES**	SOP No. **UWS-HP-606**
	Version .03
Effective Date	Page 1 of 15

Signatures and Dates:

Author:	Signatures On File
QA Review:	
Approving Authority:	

Review/Approval for unchanged documents

	Author/Date	QA Review/Date	Approving Authority/Date
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1. Purpose and Applicability

This Standard Operating Procedure (SOP) sets forth the requirements concerning all observed or apparent incidents of non-compliance with the regulations or the requirements or determinations of the Institutional Review Board (IRB) reported to the Walter Reed Army Institute of Research (WRAIR) Commander and/or IRB for human subjects research conducted at WRAIR, WRAIR Directorates, or by WRAIR personnel. These incidents may concern active or closed protocols or non-protocol issues related to WRAIR Human Research Protection Program (HRPP) policies.

Under the current regulations (21 CFR 56, 32 CFR 219, also known as the Common Rule or 45 CFR 46 [for studies receiving Department of Health and Human Services (DHHS) funding or conducted at institutions holding a Federalwide Assurance (FWA)]), the IRB has the authority to suspend or terminate approved research that is not being conducted in accordance with established requirements and regulations, or that has been associated with unexpected harm to subjects. The IRB must consider minimizing risk to research participants; protecting the informant from retaliation; protecting the reputations of the investigators and research staff until a determination is made, when appropriate; ensuring a fair process of investigation; appointing appropriate individuals to conduct the investigation; developing procedures for fact finding; documenting the investigation and the fact-finding process; determining corrective actions or sanctions and monitoring their implementation; referring matters of research misconduct to appropriate institutional officials (IOs); and reporting to department or agency heads, Sponsors, funding agencies and others (as applicable).

U.S. Food and Drug Administration (FDA) regulated research: Under 21 CFR 56.108(b), IRBs shall promptly report to appropriate IOs and the U.S. FDA, when appropriate, any instance of serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB [56.108(b)(2)]; or any suspension or termination of IRB approval [56.108(b)(3)].

DHHS or Department of Defense (DoD) regulated research: Under 32 CFR 219 and 45 CFR 46, the IRB shall promptly report any suspension or termination of approval [32 CFR 219.113 and 45 CFR 46.113] and any serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB, to the investigator, appropriate IOs, and the department or agency head.

This SOP establishes the process for receiving, investigating, managing and reporting allegations of non-compliance with regulations governing the use of

human subjects in research, IRB requirements or determinations, and/or the research protocol.

When the allegation is regarding an active protocol, the WRAIR IRB is the primary entity responsible for conducting the investigation of non-compliance. When an allegation involves other aspects of the HRPP not related to an active protocol, the WRAIR IO determines who will conduct the investigation of non-compliance. The WRAIR IRB Administrative Director and WRAIR Human Subjects Protection Branch (HSPB) may also participate in these activities, depending on the nature of the issue.

Additionally, there may be instances of non-compliance with WRAIR policies and procedures for projects deems to be “research not involving human subjects” or Exempt research, which may be considered “Institutional Non-Compliance.” This is not considered Federal non-compliance. These instances may be forwarded to the WRAIR IRB or IO for awareness and/or to demonstrate a pattern of non-compliance or educational deficits. These instances will be managed similarly to this SOP, as some findings may alter the previous risk determination.

This SOP applies to WRAIR personnel involved in human subjects research, IO, WRAIR IRB, WRAIR IRB Administrative Director, and the HSPB Staff.

2. Responsibilities:

a. When the allegation is regarding an active protocol, the WRAIR IRB is the primary entity responsible for conducting the investigation of non-compliance. The WRAIR IRB considers all allegations of non-compliance according to this SOP, and notifies all parties involved of its determinations regarding the reports of non-compliance.

b. The WRAIR IRB Administrative Director and HSPB support the WRAIR IRB in fulfilling their responsibilities.

c. When the allegation is regarding an active protocol, the IRB, the IRB Chairperson and/or IRB Administrative Director, as appropriate, will determine how the allegation will be investigated. Once the investigation is complete and the allegation has been reviewed by the IRB, the IO reviews the determination and corrective actions made by the WRAIR IRB and may require additional actions to mitigate further risk to subjects and/or research programs.

Non-compliance and unanticipated problems identified after the closure of a study may be managed in accordance with this SOP.

Non-compliance identified that relates to other aspects of the HRPP will be referred to the IO, who will determine if an investigation is warranted and the pathway to proceed.

3. Respondent Guidance and Requirements:

The respondent (PI, WRAIR research personnel, or WRAIR entity) is expected to:

a. Respond to all requests for information from the WRAIR IO, IRB or IRB Administrative Director.

b. Comply with any determinations and corrective actions made by the WRAIR IRB and the IO regarding the research.

4. Materials and Equipment:

Not Applicable

5. Procedures:

a. Reporting Allegations of Non-compliance:

1. Any individual or organization may raise an allegation of non-compliance. Such allegations would be considered as described below.

2. Allegations of non-compliance made in good faith will not reflect negatively on the reporting individual, nor lead to reprisal against that individual.

3. Allegations of non-compliance should be reported as soon as possible.

4. Allegations of non-compliance may be submitted verbally or in writing (via mail or email) to the WRAIR IRB, HSPB, or IO. The identity of the individual making an allegation of non-compliance will be kept confidential to the extent possible. Disclosure will be limited to those who need to know, consistent with a thorough, competent, objective and fair proceeding, except as otherwise prescribed by applicable law.

5. Allegations of non-compliance should include a description of the possible noncompliance, including the protocol title, number, date, time, personnel involved and reporting person's name and contact information, if available.

6. Potential sources from which allegations of non-compliance may come could be, but are not limited to:

   a) Research participants or their friends or family [for example: participant's legally authorized representative];

   b) DoD Research Monitor (if applicable);

   c) Reports of protocol non-compliance (including, but not limited to: deviation reports, continuing review reports, information from sponsor's monitoring letters or other correspondence);

   d) Findings discovered during routine compliance monitoring (Refer to WRAIR SOP UWS-HP-633);

   e) Failure or repeated failures of the investigator to file requested reports to the WRAIR IRB;

   f) Institutional personnel;

   g) Publications involving WRAIR investigators engaged in human subjects research without WRAIR IRB approval of the referenced study or studies;

   h) Office of Human Research Protections (OHRP) or US FDA warning letters/debarment regarding an investigator or a study;

   i) Media or anonymous sources.

b. Receipt and Investigating Allegations of Non-compliance:

1. Upon receipt of an allegation of non-compliance involving human subjects research, the WRAIR personnel receiving the report (e.g. HSPB staff, IRB member, IO) promptly notifies the WRAIR IRB Administrative Director (or designee), if not already informed. HSPB staff logs the initiation of the report in the database for the study, as applicable. (Appendix A is utilized to record, in as much detail as possible, the information received.)

2. The initial report is promptly (within 48 hours) provided to the IRB Chair (or designee), and IRB Administrative Director, as applicable, for preliminary review. The IO will be contacted by the IRB Chair or the IRB Administrative Director for any allegations that could impact subject safety or willingness to continue in research. PIs are strongly encouraged to report to their

leadership immediately upon discovery of potential non-compliance. The preliminary review involves the following three questions:

a. Is the allegation credible?

b. Does the allegation fit within the scope of the IRB's purview? (HSPB may advise if there are any questions about the purview of the IRB and/or scope of the WRAIR HRPP.)

c. Does the allegation involve possible serious or continuing non-compliance?

If the answer is "yes" to all of the questions above, an investigation of non-compliance will occur as outlined below.

If the answer to questions a or b is "no," the matter should be dismissed or referred to a more appropriate entity for consideration (e.g., allegations concerning scientific misconduct should be referred in accordance with WRAIR Command Policy Memorandum for Scientific Misconduct).

If the answer to both questions a and b is "yes," but the answer to c is "no," the WRAIR IRB should proceed with the matter as an issue involving non-compliance that is neither serious nor continuing (see SOP UWS-HP-621, Deviation and Unanticipated Problems Reporting).

3. Based on the nature and substance of the allegation or expertise required during the investigation, the IRB Chair, IO, and/or IRB Administrative Director, as appropriate, may delegate the investigation to an experienced IRB member, and experienced IRB staff person, a subcommittee, or other qualified individuals. Experienced IRB members are usually members with two or more years of experience serving on an IRB or with specific expertise on the subject to conduct the investigation. Consultants may also be involved. The WRAIR IRB Chair or designee determines if immediate suspension of subject enrollment is required to protect the rights, safety and welfare of subjects until the allegation is investigated. If immediate suspension is necessary, this will be reported to the IO and to the fully convened IRB at the next scheduled meeting.

4. Investigation of non-compliance:

a. Investigation of possible non-compliance related to active protocols.

The WRAIR IRB has the primary responsibility for conducting an investigation of noncompliance that is related to active protocols, including those in data analysis only. In most circumstances, the IRB is responsible for assessing the possible non-compliance, and as part of the information gathering stage, collecting information (as necessary) and otherwise engaging in actions necessary to investigate the possible noncompliance. The IRB may request assistance from the HSPB. In some cases, an *ad hoc* IRB subcommittee may assist in the assessment and information gathering. In cases where an investigation of noncompliance is related to an active protocol, the IRB is the principal entity that makes determinations about noncompliance and provides their determination and corrective actions to the IO.

b. Investigation of possible non-compliance NOT related to an active Protocol (closed protocol or other HRPP aspect).

   The IO determines who will conduct the investigation of non-compliance not related to an active protocol. The IO may appoint a subcommittee or other qualified individuals for this purpose. The IO may consult with other WRAIR officials in making this decision, including the IRB Chair (or designee), and IRB Administrative Director.

   The IRB Chair (or designee) or IRB Administrative Director will notify the PI or the WRAIR personnel or entity, if any, against whom an allegation of non-compliance is made, in writing, of the allegations and the process of investigation of non-compliance within **5 working days** of performing a preliminary review of non-compliance, if the preliminary review finds that an investigation of non-compliance is needed.

5. Information-gathering stage: Additional information regarding the report is obtained by the investigation designee including, but not limited to, the following:

a. Interviews or inquiries with the authors of the allegation of non-compliance report or complaint;

b. Written requests for follow-up with the authors of the allegation of noncompliance report or complaint, Sponsor, Monitor or other regulatory person;

c. Discussions with the PI or other study personnel;

d. Discussions with subjects and/or their legally authorized representatives;

e. Requests of records from the PI or study personnel;

f. Request of IRB Directed (For Cause) monitoring (Refer to WRAIR SOP UWS-HP-634).

The IRB Chair, fully convened IRB, WRAIR IRB Administrative Director, or a subcommittee may determine that a directed (for cause) review is merited. If so, the review will be conducted as soon as possible, but within a time frame, commensurate with the seriousness of the allegations and geographical location of the study site and/or investigator (Refer to WRAIR SOP UWS-HP-634, Directed Monitoring).

The IRB or the IRB Administrative Director may elicit assistance from local points of contact (POCs), such as the regulatory affairs staff, that assists with the conduct of research at the satellite sites, for the purposes of the directed-review and investigation, to include facilitating remote access to records (Refer to the WRAIR HRPP).

Protocol Investigators and others who may have relevant information should have the opportunity to provide input during the investigation. Every effort must be made to protect the identity of Institutional Personnel (also known as “Whistleblowers”) before, during, and after an investigation.

At the conclusion of this stage, the additional information will be summarized in an evaluation report with summary or source documents (if pertinent). This evaluation report does not make conclusions or result in a determination of noncompliance. The evaluation report will be shared with the respondent (to the extent permitted by law and WRAIR policy).

6. IRB formal determinations: The WRAIR IRB will assess the possible non-compliance and information gathered about the possible non-compliance (including, but not limited to, the evaluation report) at the earliest convened IRB meeting that ensures that the respondent and IRB members have had sufficient time to review the pertinent information. The IRB may need to schedule additional IRB meetings, in addition to its regularly scheduled meeting(s), to address the possible non-compliance in a timely manner.

If the respondent wishes to provide written materials, the materials must be provided to the IRB **at least 5 working days** before the meeting. All reports, documents and written materials will be provided to the entire IRB.

If the IRB adds allegations to those already communicated to the respondent, or obtains additional information than that which is provided in the evaluation report (if any), the respondent must be provided with a copy of these new allegations and/or additional information (to the extent permitted by law and WRAIR policy), and the respondent must be given an opportunity to respond.

7. Those against which allegations of non-compliance have been made will be provided a description of the allegations, evaluation report, reasonable access to evidence (to the extent permitted by law and WRAIR policy) and an opportunity to respond and provide input.

At the convened meeting, the IRB will review all information provided and decide whether more information is needed. It will give the respondent an opportunity to respond to the allegations. The respondent may bring an advisor, colleagues or other support staff (as guests, not to represent the respondent) to the IRB meeting, if the IRB is notified at least 48 hours in advance of the meeting. A confidentiality requirement may be imposed as appropriate, consistent with law or WRAIR policy.

At the same or a subsequent convened meeting (should additional information be needed), the IRB will make a determination of whether the evidence represents serious and/or continuing non-compliance, and what, if any, additional IRB action is required. The IRB will vote and document its determinations and corrective actions in the meeting minutes. The IRB will communicate its decisions to the respondent and other appropriate WRAIR officials.

8. The convened WRAIR IRB reviews unanticipated problem reports in accordance with SOP UWS-HP-621, Deviation and Unanticipated Problem Reporting. The IRB may recommend further investigation of non-compliance as part of its determination and action plan. This may occur, for example, if the IRB recalls previous problem reports that, in conjunction with the current report, might represent continuing non-compliance. Such further investigation would proceed in accordance with this SOP.

9. If the investigation fails to support the allegation and no evidence or other instances of non-compliance is identified, the investigation results will be reported to the IO and IRB Administrative Director. The IO in consultation with the IRB Chair and IRB Administrative Director may require an additional

investigation and/or referral of the investigation to the IRB or other officials, as applicable.

10. The convened IRB will review all information provided. The IRB will:

a. Determine if the investigation was sufficient. If the IRB determines that the investigation was not sufficient, it may require additional investigation before making a determination regarding non-compliance. Alternately, the IRB may refer the investigation to the next higher authority (HQ USAMRDC ORP HRPO) for further investigation if there is an institutional conflict of interest.

b. If the IRB finds that there is non-compliance, the IRB must determine if the non-compliance is serious and/or continuing.

c. Review and determine actions to correct the non-compliance [see section B (1)]. The IRB must take into account the situation and identify actions that are appropriate given the seriousness and extent of the non-compliance. The IRB must identify a well-defined timeline for the corrective action plan. When required by the IRB, the PI will develop and provide for review by the IRB a corrective action plan for the non-compliance.

d. IRB meeting minutes must reflect the determination of the IRB with regard to non-compliance and include the corrective action plan for review by the IO.

e. Study investigators must be promptly provided written notification of the IRB's determination along with a statement of the reasons for its decision and corrective action plan as stipulations. Study investigators must have an opportunity to respond to the IRB's determination and corrective actions in person or in writing.

11. Managing Non-Compliance.

a. Appropriate corrective action must be taken to assure the safety and welfare of human research subjects and the integrity of the research after an IRB determination of serious and/or continuing non-compliance is made. The IRB must identify appropriate actions and a timeframe for the respondent to provide responses to these actions; such actions may include, but are not limited to:

1) Suspension or termination of the research;

2) Temporary suspension of new subject enrollment in a protocol;

3) Notification to subjects of serious or continuing non-compliance;

4) Requiring the investigator to destroy or return all data from research involving subjects obtained without IRB review and approval;

5) Requiring the investigator to make all data anonymous by removing all codes, identifiers, and identifiable information;

6) Requiring the PI and/or study staff training in Good Clinical Practices, or alternative human subjects protection training;

7) Requiring investigator supervision by a qualified mentor and /or hiring of new, qualified staff;

8) Imposing sanctions on the respondent;

9) Suspending individual investigators from participation in the research protocol;

10) Requiring modifications to the protocol or consent form;

11) Re-consenting subjects and/or consent monitoring;

12) Requiring additional safeguards such as more frequent IRB continuing review, third party monitoring, or auditing of research/consent process/recruiting and/ or site visits;

13) Notifying sponsors, funders, partners, or collaborators of the findings of serious and/or continuing non-compliance and/or required corrective actions, if applicable;

14) Additional decisions may be needed regarding the status of data/specimens collected and the appropriateness of publishing the study results;

15) Other actions as appropriate.

b. Should the IRB determine that the incident is isolated and resolved, a memorandum will be sent from the IRB to the PI (and copied to the sponsor, IO, and other involved agents) describing resolution based on the

documentation and results of the investigation. Suspension of enrollment, if any, is lifted. Should the IRB determine a new continuing review interval, this date will be stated in the letter.

c. Should the IRB make a determination of serious and/or continuing non-compliance the PI will be sent a separate communication detailing the IRB's determination, length of suspension (if any) or termination of IRB approval, corrective action plan, any additional requirements, sanctions or restrictions and a request for a response in writing.

d. The IRB, HSPB staff or IRB Administrative Director must document that all corrective actions have been completed in a satisfactory manner and timeframe. The IO will be provided this documentation and may impose additional corrective actions or sanctions for investigators who fail to satisfactorily complete required corrective actions in the allotted timeframe.

e. Regarding Suspensions:

The WRAIR IRB Chair or designee determines if immediate suspension of subject enrollment is required to protect the rights, safety and welfare of subjects until the allegation is investigated.

The length of any suspension is determined by the WRAIR IRB Chair, or fully convened IRB, and communicated to the IO. The length of suspension is based on the seriousness of the preliminary information received or determined non-compliance. The IO can request additional time be added to the suspension, but they cannot request a shorter suspense than determined by the WRAIR IRB Chair or fully convened IRB.

If a suspension is merited, a meeting between the IRB Administrative Director or WRAIR IRB Chair and PI is called within 30 days of the notification of suspension. The PI will develop a corrective action plan for review by the convened IRB, if required.

Should the IRB determine to suspend the protocol either singly, or in conjunction with other protocols under the same PI or site, the WRAIR IRB Chair, IOs or designees notify the following (as applicable): PI, Co-PIs, Department Chief, Branch and/or Center/Directorate Director, IO, Chief Science Officer, USAMRDC ORP HRPO, Army Human Research Protections Office (AHRPO), funders and sponsors. This notification is made by telephone, fax, or email, and may be followed by mail.

c. Reporting Non-Compliance:

1. Once the IRB of record makes a finding of serious non-compliance and/or continuing non-compliance, the findings must be promptly reported to the HQ USAMRDC ORP HRPO regardless of the risk level of the study or the type of HQ level review the study received. Notifications are done by phone to the Director, ORP HRPO, followed by a written notification/communication. (See Appendix B for required reporting information)

2. Findings of serious and/or continuing non-compliance must also be promptly reported to the AHRPO in accordance with DODI 3216.02. Notifications are done by phone to the Director, AHRPO, followed by a written letter. All findings of serious and/or continuing non-compliance will be reported through AHRPO to the Director, Defense Research and Engineering in accordance with DoDI 3216.02.

3. As appropriate, other federal agencies such as the OHRP or US FDA may require prompt reporting of findings of serious and/or continuing non-compliance. Reporting to these agencies will depend on the funding for the study under which non-compliance was determined and/or whether the study is subject to US FDA regulations. It is the responsibility of the IO to ensure reporting to these agencies in accordance with OHRP and US FDA regulations.

4. For US FDA regulated studies sponsored by the Office of The Surgeon General of the Army, the US FDA will be notified by the USAMRDC of any determination to further suspend or terminate approval.

5. Non-HRPP issues. The investigation of possible non-compliance may uncover issues that are not under the HRPP purview of the HSPB or the IRB (e.g. poor record keeping or inadequate procedures not related to the human subjects research). The IRB or the IRB Administrative Director may refer these concerns to other appropriate entities within WRAIR, such as the IO, Chief Science Officer, and others, to address appropriately, consistent with applicable regulations and WRAIR policies.

d. Any response from the respondent, US FDA, OHRP, USAMRDC ORP HRPO, sponsor or other involved persons will be reviewed by the IRB Chair, fully convened IRB, and IO.

e. Copies of all correspondence and reports are maintained in a separate file in the HSPB.

6. Explanation of Abbreviations, Acronyms, and Definition of Terms

Abbreviations and acronyms have been defined in the text at the time of first use.

7. References

Reference Number or Authors	Document Title
AR-40-7	Use of Food and Drug Administration – Regulation Investigational Products in Humans Including Schedule I Controlled Substances, 19 October 2009
AR 40-68	Clinical Quality Management, 26 February 2004
AR 70-25	Use of Volunteers as Subjects of Research, 25 January 1990
DODI 3216.02	Department of Defense Instruction- Protections of Human Subjects and Adherence to Ethical Standards for DOD Supported Research, 15 April 2020
ICH GCP E6	Guideline for Good Clinical Practice.
OHRP Guidance	*Guidance on Reporting Incidents to OHRP*, 20 June 2011
OHRP Guidance	*Guidance on Written IRB Procedures*,1 July 2011
Titles 21, 32 and 45	Code of Federal Regulations
USAMRDC Policy 16	Investigating, Managing, and Reporting Noncompliance with Human Subjects Research Regulatory Requirements
5 USC 2302(b)(8)	Whistleblower Protection Program
WRAIR HRPP	WRAIR Human Research Protections Program (HRPP)
WRAIR IRB Charter	Walter Reed Army Institute of Research Institutional Review Board (WRAIR IRB) Charter
WRAIR SOP UWS-HP-621	Deviation and Unanticipated Problem Reporting

WRAIR SOP UWS-HP-633	Routine Monitoring for Human Subjects Research Compliance
WRAIR SOP UWS-HP-634	Directed (For Cause) Monitoring of Human Subjects Research

7. Appendices and Attachments

Appendix or Attachment Number	Title
Appendix UWS-HP-606-A	Allegation of Non-Compliance Intake Form
Appendix UWS-HP-606-B	Elements of a Non-Compliance Report
Appendix UWS-HP-606-C	Non-Compliance Process Checklist

8. Document Revision History

Version Number	Brief Description of Changes	Effective Date
.00	New	15 Dec 2006
.01	Biennial review, revised to update organization names, incorporate relevant regulations, and include updated policies and procedures.	14 Jan 2009
.02	Biennial review, revised to incorporate relevant regulations, and include updated policies and procedures.	17 Feb 2012
.03	Review and revisions to incorporate updated guidance, policies and regulations and AHRPO audit requirements.	07 March 2022