SOP Title	**Safety Reporting for Clinical Trials**	SOP No.	**UWS-HP-619**
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Signatures and Dates:

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1. Purpose and Applicability

This standard operating procedure (SOP) outlines the process for documentation and review of safety reports, and exceptions to safety reporting/documentation within the context of a clinical trial where a drug, biologic, device, or combination product is being used or evaluated as the primary focus of the study.

A safety report includes any of the following: serious adverse event (SAEs) (related & unexpected) / serious unexpected suspected adverse reaction (SUSAR) reports (an investigator's initial, follow-up, final report, DoD Research Monitor independent report), an unanticipated adverse device effect (UADE), summary from a Data and Safety Monitoring Board (DSMB)/Independent Data Monitoring Committee (IDMC)/Safety Monitoring Committee (SMC) or Sponsor's safety reports submitted to the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), or other countries' regulatory agency overseeing the investigational product being used in the study, or a report of a clinical hold/study halt notification. The reporting of unanticipated problems and deviations is covered under a separate SOP, UWS-HP-621, Deviation and Unanticipated Problem Reporting.

This SOP specifically outlines reporting requirements for safety reports, which include unanticipated serious adverse events or unanticipated serious adverse device effects reporting in the context of a clinical trial where a drug, biologic, device, or combination product is being used or evaluated as the primary focus of the study. There are times when a SAE/SUSAR or an UADE may also be considered an unanticipated problem involving risks to subjects or others (UPIRTSO). If a SAE/SUSAR or UADE meets the definition of an UPIRTSO, then this safety report will also need to be triaged, reviewed and reported as a potential UPIRTSO as per SOP UWS-HP-621, Deviation and Unanticipated Problem Reporting.

This SOP applies to the Human Subjects Protection Branch (HSPB) staff, the WRAIR Institutional Review Board (IRB), investigators, DoD Research Monitors, and WRAIR Commander (Institutional Official; IO). This SOP applies the US FDA definitions and requirements, as they are the most stringent, and is applicable to all clinical trials involving drugs, biologics, devices or combination products.

2. Background and Investigator Guidance

The WRAIR IRB ensures that the safety monitoring plan and reporting requirements are outlined in the research protocol and are appropriate to the planned research. The IRB-approved protocol language supersedes this SOP.

a. Safety Monitoring Plan

Prior to submitting protocols to the WRAIR IRB, Principal Investigators (PIs) and the Sponsor should ensure that DSMBs/IDMCs/SMCs (if applicable) are established and that a safety monitoring plan and DSMB/IDMC/SMC charter is included with their initial submission for initial triage by the WRAIR HSPB. The safety monitoring plan for Phase I clinical trial studies may be included within the protocol. The collaborative plans between the PI and Sponsor should be robust and commensurate with the degree of risk expected to be incurred by study participants and the vulnerability of the study population. The safety monitoring plans must outline the expectations for safety reporting.

Before research is approved, the WRAIR IRB receives the safety monitoring plan and gives appropriate consideration to the spectrum of potential, expected and unexpected safety-related elements that might be anticipated to occur in study subjects. These safety reporting elements may include or be inclusive of:

1) Adverse Events (AEs)
2) Serious Adverse Events (SAEs)
3) Adverse Reactions (ARs)
4) Serious Unexpected Suspected Adverse Reactions (SUSARs)
5) Serious Adverse Device Effects (SADEs), and
6) Unanticipated Adverse Device Effects (UADEs)

The WRAIR IRB is responsible for the review and approval of the safety monitoring plan and ensuring the reporting requirements are outlined in the research protocol and are appropriate to the research.

b. Safety Reports

Safety report requirements are based on multiple National, International and Organizational definitions and guidance for clinical trials involving drugs, biologics, devices, and combination products. If there are conflicting requirements by one or more organizational policy or guidance, the general default is to apply the US FDA regulations or guidance.

A full-cycle safety report includes a PI's initial, follow-up(s), and final report. Reports may include a description of events, surrounding circumstances and any corrective action plans or measures taken to address the events.

In addition to PI descriptions of events, reports may include summaries or identifications of events and information from:

1) DoD Research Monitor independent reports

2) Participants
3) An unanticipated adverse device effect and summary from a DSMB/IDMC/SMC
4) Sponsor's safety reports submitted to the FDA, EMA, or other countries' regulatory agency overseeing the product being used in the study, or
5) A report of a clinical hold/study halt notification.

c. The Principal Investigator (PI) is advised to:

1) Ensure that a DSMB/IDMC/SMC (if applicable) is established when submitting protocols to the WRAIR IRB and ensure that a safety monitoring plan and DSMB/IDMC/SMC charter is included with the initial submission to the WRAIR IRB for review and approval.
2) Ensure that a Research Monitor and/or alternate Research Monitor is/are assigned in accordance with the requirements of the Department of Defense (DoD) Instruction 3216.02 for studies anticipated to be greater than minimal risk and supported by the DoD (funding, resources, personnel, etc.).
3) Promptly submit any SAEs/SUSARs, unexpected AEs/ARs, and UADEs, subject withdrawals, pregnancy notifications, clinical hold/study halt notifications, as applicable, to the WRAIR IRB via the WRAIR HSPB, including associated DoD Research Monitor reports, and safety summaries from the DSMB/IDMC/SMC during the course of the trial and at the time of continuing review.

   Timing Expectations for Prompt Safety Report Submissions:

   a. During the course of the trial and at the time of continuing review, reports must promptly be submitted to the WRAIR IRB via the WRAIR HSPB, for AEs, SAEs, ARs, SUSARs, ADEs, UADEs, subject withdrawals, pregnancy notifications, and clinical hold/study halt notifications, along with associated DoD Research Monitor reports, and safety summaries from the DSMB/IDMC/SMC.
   b. All subject pregnancies and subject withdrawals should be reported to the IRB within 48 hours of the PI being notified, regardless of relatedness, unless otherwise stated in the protocol. The IRB Chair (or Designee) will determine which reports should be forwarded to the full board.
   c. All study deaths should be reported to the WRAIR IRB within 48 hours of the PI being notified, regardless of relatedness. The IRB Chair (or Designee) will determine which reports of subject deaths should be forwarded to the full board.

d. When PIs become aware of Clinical Holds or Study Halts, PIs shall report by telephone, facsimile or email, within 24 hours, information as it becomes available, pertaining to the circumstances of the Hold or Halt.
e. Serious, Unexpected and Suspected Adverse Events:

1. When PIs become aware of events, prompt reporting (within 48 hours) is required by telephone, facsimile or email for events that meet the following criteria:

a) SERIOUS (delineated in the safety monitoring plan), and/or
b) UNEXPECTED (not delineated in the safety monitoring plan) and/or
c) SUSPECTED (based on the PIs clinical judgement).

2. Follow-up in writing is required within 10 working days from knowledge of the event. Failure to report events/reactions that meet any of the above-described criteria is considered non-compliance (refer to WRAIR SOP UWS-HP-606, Non-Compliance Procedures).

4) In addition to the WRAIR IRB reporting requirements outlined above, submission of reports will be made to the Sponsor in accordance with the Sponsor's requirements, and to the US FDA as required by the US FDA reporting requirements in 21 CFR 312 and 812.
5) PIs are expected to respond to documentation and information requests from the WRAIR IRB and WRAIR HSPB in a timely manner.
6) PIs are responsible for maintaining the correspondence with the reviewing IRBs, Sponsors, and regulatory authorities, as appropriate.
7) Failure to report SAEs/SUSARs meeting any of the above-described criteria is considered non-compliance (refer to WRAIR SOP UWS-HP-606, Non-Compliance Procedures).
8) Devices: When PIs becomes aware of UADEs, prompt reporting (within 48 hours) is required by telephone, facsimile or email. PIs must follow-up in writing within 10 working days from knowledge of the event.
9) Failure to report UADEs is considered non-compliance (refer to WRAIR SOP UWS-HP-606, Non-Compliance Procedures).
9) Submit any SAEs/SUSARs, unexpected AEs/ARs, UADEs, as applicable, to the Sponsor in accordance with the Sponsor's requirements and to the US FDA as required by the US FDA reporting requirements. These requirements are in addition to reporting to the WRAIR IRB.
10) Investigators shall report by telephone, facsimile or email (within 24 hours) clinical holds or study halts when s/he becomes aware of the event and provide additional information as it becomes available.

11) Investigators should request prior IRB-approval of exceptions to the safety monitoring plan (e.g., stopping/halting rules) whenever possible unless immediate action is needed to protect the rights, welfare, and safety of study subjects. If immediate action is taken, this must be reported to the IRB/HSPB within 24 hours.
12) Respond to requests for documentation and information from the WRAIR IRB and WRAIR HSPB.
13) Maintain correspondence with the reviewing IRBs, Sponsor, and regulatory authorities, as appropriate.

Note: The reporting of unanticipated problems and deviations is covered under a separate SOP, UWS-HP-621, Deviation and Unanticipated Problem Reporting.

3. Responsibilities

a. The HSPB Human Subjects Protection Scientist (HSPS) Point of Contact (POC) is the HSPB staff member assigned to review the protocol and manage the IRB documentation for that study, to include all safety reports submitted for review. The HSPB POC is responsible for filling out the Safety Reporting Action Sheet (Appendix A) and submitting the safety report with the completed Safety Reporting Action Sheet to the WRAIR IRB Chair (or Designee) for review. If the safety report is referred to the fully convened WRAIR IRB, the HSPB POC is responsible for scheduling the report for the meeting and preparation of all communications with the study team.

b. The WRAIR IRB Chair (or Designee) reviews the safety reports and exceptions to the safety monitoring plan and takes appropriate action.

c. The WRAIR IRB Administrator reviews the safety reports and exceptions to the safety monitoring plan as outlined below for protocols where the WRAIR is relying on another institution for their IRB review, and acknowledges receipt of information and notes the action that the other IRB has taken.

d. The WRAIR IRB ensures an adequate safety plan for all protocols approved by the IRB, and reviews safety reports referred from the WRAIR IRB Chair (or Designee) for a fully convened IRB Review. The IRB assesses appropriate action for any issues cited in the report to ensure the safety of study participants.

e. PIs are responsible for submitting the safety reports to the WRAIR IRB as per the reporting requirements outlined in the protocol and safety monitoring plan.

f. DoD Research Monitors (and their designated alternates) are a DoD unique requirement and are appointed to assist the IRB with issues of individual subject/participant management and safety. Herein referred to as "Research Monitor".

g. The WRAIR Commander (IO) approves exceptions to the safety monitoring plan.

4. Materials and Equipment

Not applicable

5. Procedures

a. Prior to Protocol Approval:

1) Prior to protocol approval, the WRAIR IRB gives appropriate consideration to the spectrum of suspected adverse reactions that might be anticipated to occur in study subjects. A safety monitoring plan should be developed by the Sponsor and investigator and submitted as part of the protocol. This plan should be robust and commensurate with the degree of risk expected to be incurred by study subjects and the vulnerability of the study population. The WRAIR IRB is responsible for the review and approval of the safety monitoring plan.
2) Formal safety review is outside the scope of the WRAIR IRB because the IRB may not have the expertise to serve as a safety monitoring board. However, the IRB does have a duty to ensure that the Sponsor's safety officer, the designated DoD Research Monitor (and alternate Research Monitor as appropriate), and/or the DSMB/IDMC/SMC assigned to safety oversight of a particular clinical trial are impartial and qualified to perform its safety assessment.
3) Safety Charter and Monitoring Committee:
   a) A safety monitoring charter should include a list of members serving on the safety committee and their qualifications, and must be provided to the WRAIR IRB as part of the protocol submission for review.
   b) All DSMBs, IDMCs, or SMCs should have at least one impartial member. It is recommended that the DoD Research Monitor and/or alternate serve as a member of the DSMB/IDMC/SMC.
   c) Conflict of interest statements for all safety committee members should be maintained in the Sponsor's regulatory file (Investigator's regulatory file for Investigator-initiated research), and be available to the IRB upon request.

4) In accordance with the DoD Instruction (DoDI) 3216.02, all DoD-conducted research studies determined to be greater than minimal risk [as defined by 32 CFR 219.102(i)] require the appointment of an independent DoD Research Monitor by the IRB. (Note: At the discretion of the IRB, a DoD Research Monitor may also be assigned for minimal risk studies. This individual may be identified by the investigator, IRB or IO).

b. WRAIR HSPB POC Receipt and Initial Review of Safety Reports

1) Safety reports are initially received by the HSPB POC for that study. The HSPB POC provides the safety report, including additional documentation (i.e., Sponsor's opinion and the DoD Research Monitor's report) and the corresponding Safety Reporting Action Sheet (see Appendix A) to the WRAIR IRB Chair (or Designee) for review and submits to the fully convened WRAIR IRB, as appropriate, for review.
2) The reviewed Safety Report Action Sheet is placed in the respective study file; the Safety Report Action Sheet is intended for internal use only and is not provided to the PI and/or study team. An email acknowledgement/acceptance is sent to the PI and/or appropriate study team members. Emails are also sent to obtain additional information and documentation for review of a safety report.

c. WRAIR IRB

1) A health care provider member of the IRB or the IRB Chair (in consultation with a health care provider member of the IRB) is responsible for:
   a) Reviewing all safety reports.
   b) During their review, determining if any SAE/SUSAR or UADE meet the criteria for an UPIRTSO.
   c) Review all clinical hold/study halt notifications made by the Sponsor, DoD Research Monitor, etc. and request additional information from the study team as appropriate.

2) The WRAIR IRB Chair (or Designee) takes appropriate action(s) at his/her discretion through:
   a) Requests for additional information;
   b) Referring to the full WRAIR IRB for review;
   c) Referring to the full WRAIR IRB for information only;
   d) Acceptance with no further action required;
   e) Acceptance with minor corrections to the safety reports;
   f) Acceptance with required modification to protocol-related documents;

g) Referring for review as an UPIRTSO; or
h) No actions/file only. (See Appendix A)

SAEs/SUSAR reports, UADE reports, are paired up by the HSPB POC with the DoD Research Monitor reports and any subsequent follow-up and final reports, to provide additional context for final disposition.

3) IRB Review of Reports
   a) All summary safety reports from the Sponsor or Sponsor-designated DSMB/IDMC/SMC are initially reviewed by the WRAIR Chair (or Designee), and then provided to all IRB members for review or information only. These are generally provided in real time for IRB Chair (or Designee) review and then with the continuing review submissions for the fully convened WRAIR IRB unless there are some major safety issues identified in the reports, at which point they would be referred to the fully convened WRAIR IRB in real time.
   b) All clinical hold/study halt notifications are initially reviewed by the WRAIR IRB Chair (or Designee), and then provided to all IRB members for review or information only, depending on the nature of the hold/halt.
   c) The WRAIR IRB will use the Review Form in Appendix D of SOP UWS-HP-621 to review the safety report and determine if any additional information needs to be provided and if any corrective actions need to be taken, such as revising the protocol and/or consent form and other supporting documentation.
   The WRAIR IRB will also indicate what reporting is required for the event:
      1. Refer to the U.S. Army Medical Research and Development Command, Office of Research Protections, Human Research Protections Office (USAMRDC ORP HRPO) for review and approval;
      2. Notify the IO, who reports to the U.S. Department of Health and Human Services, Office of Human Research Protections (DHHS OHRP) or the Army Human Research Protections Office (AHRPO), as appropriate;
      3. Submit to TSG Sponsor's Representative;
      4. Submit to US Department of Health and Human Services (HHS) Office of Human Research Protections (OHRP); and/or
      5. No further reporting required.

4) Safety Reports Requiring Fully Convened WRAIR IRB Review
The following outlines the criteria for a fully convened IRB review of safety reports:
   a) Related and Unanticipated SAEs/SUSARs for an investigational product, determined by the WRAIR IRB Chair (or Designee) to require full board review. All other related WRAIR Site SAEs/SUSARs will be provided to the fully convened WRAIR IRB for information purposes only;
   b) All UADEs for an investigational device;
   c) All deaths as requested by the IRB Chair (or Designee); and
   d) Any SAE/SUSAR or UADE determined to also meet the criteria for an UPIRTSO (will also be triaged under SOP UWS-HP-621, Deviation and Unanticipated Problem Reporting).

5) IRB Appointment of DoD Research Monitors
   a) The IRB is responsible for appointing and/or approving an independent DoD Research Monitor by name for greater than minimal risk (GTMR) human subjects research. This requirement applies to DOD–conducted research.
   b) The IRB appointee(s) shall meet the minimum roles and responsibilities defined in the DODI 3216.02, Enclosure 3, Section 8, and ensure that the DoD Research Monitor(s) duties are based on the specific risks or concerns about the research. The IRB shall document:
      1. Approval of a written summary of the DoD Research Monitor's duties, authorities, and responsibilities. This may be accomplished thru the IRB approval of the protocol when the DoD Research Monitor's duties are defined within the protocol.
      2. Communicating with the DoD Research Monitor to confirm their duties, authorities, and responsibilities. This may be accomplished through communication to the DoD Research Monitor in the official IRB Approval memorandum and/or Commander Approval Authorization memorandum.
      3. Case-by-case consideration on a waiver to the requirement to have a DoD research monitor when the inclusion of a DoD Research Monitor is not necessary to provide additional protections for human subjects.
   c) Procedures specific to the role of DoD Research Monitors include discussions on research progress with the PI, interviewing subjects, consulting on individual cases, and/or evaluating suspected adverse reaction reports on behalf of the IRB. DoD Research Monitors:

1. At the direction of the IRB, oversee clinical trial procedures (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units); oversee study interventions and interactions; review safety monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis.
2. Promptly report discrepancies or problems to the IRB.
3. Have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the DoD Research Monitor's report.
4. Review all unanticipated problems involving risks to subjects or others (UPIRTSOs, as outlined in SOP UWS-HP-621, Deviation and Unanticipated Problem Reporting), SAEs/SUSARs, unanticipated adverse device effects, and all subject deaths, and provide an unbiased written report of the event promptly (within 48 hours) to the WRAIR IRB by email (usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil), or by facsimile at (301) 319-9961.

If the event is determined to be related, the DoD Research Monitor or their approved alternate, will then submit written reports within 10 working days to the WRAIR IRB. If the event is determined not be related, the DoD Research Monitor's written report will be provided to the PI to file with the event report in the protocol regulatory binder.

6) IRB Authority to Waive the DoD Research Monitor Requirement:
Exceptions to the DoD Research Monitor Requirement:
   a) DOD Components have the authority to waive the DoD Research Monitor requirement when a DoD Research Monitor is not necessary to provide additional protections. For WRAIR, the authority for granting a waiver is under the purview of the IRB Chair. The specific criteria used to evaluate the appropriateness of a DoD Research Monitor waiver is:
      1. The research is permanently closed to the enrollment of new subjects; and
      2. The research remains active only for long-term follow-up of subjects, or data analyses.
      3. Long-term follow-up may include interactions with subjects, collection of data from the subject's routine clinical (i.e. non-research) treatment and monitoring, or minimal risk research interventions eligible for expedited review in accordance with the

Common Rule and Federal Register (e.g., noninvasive collection of biospecimens for research purposes); and

4. Remaining research activities involve no greater than minimal risk to subjects.

b) This waiver also applies to human subjects research conducted by non-DOD institutions where Army support is added to a protocol after the above-named criteria are met, such as when an Army award is used to fund a study that is only open for data analysis at the time the award is issued.

c) The waiver must be documented in the IRB minutes. In the case where the IRB services more than one DOD institution or reviews on behalf of another DOD institution, the IRB will coordinate whether the waiver provision is acceptable at that DOD institution. In the case where the IRB chooses to review a protocol that is otherwise eligible for expedited review procedure at a convened board meeting, the waiver may be implemented.

d) The DA institution supporting the project must verify that appropriate local ethical requirements governing the proposed non-DOD research have been satisfied.

7) Exceptions to the Safety Monitoring Plan

a) Any alterations or exceptions to safety monitoring plans or reporting expectations should be requested by PIs prior to IRB-approval whenever possible unless immediate action is needed to protect the rights, welfare, and safety of study subjects**.** If immediate action is taken, this must be reported to the IRB/HSPB within 24 hours.

b) Review by the WRAIR IRB:

1. Requests for exceptions to the safety monitoring plan (e.g., waivers for stopping/halting rules) are initially received by the HSPB HSPS for that study. The HSPB HSPS provides the request to the WRAIR IRB Chair (or Designee) for review and approval. This review is performed by a health care provider IRB Chair Designee.
2. The WRAIR IRB Chair (or Designee) may request additional information from the DoD research monitor, DSMB/IDMC/SMC, and others, where appropriate, before providing an approval to the WRAIR Commander (IO).
3. The WRAIR IRB Chair (or Designee) may provide a verbal exception (eligibility) immediately if necessary, to protect the rights, welfare, and safety of the study subject. If an exception is granted, follow-up documentation must be provided in writing within 5 calendar days (NOT business days).

4. All exceptions to the safety monitoring plan are accepted and approved by a written memorandum from the WRAIR IRB Chair (or Designee) and provided to the WRAIR Commander (IO) for approval authorization.

d. WRAIR IRB Administrator Review of Safety Reports (WRAIR IRB is Not the IRB of Record)

1) Safety reports for studies, where the WRAIR IRB is Not the IRB of Record and they rely on another institution for IRB review, are reviewed by the WRAIR IRB Administrator (or Designee). The HSPB POC provides the safety report, including additional documentation (i.e., Sponsor's opinion, the DoD research monitor's report, and the reviewing IRB's action regarding the safety report) and the corresponding Safety Report Action Sheet (see Appendix A) to the WRAIR IRB Administrator (or Designee) for review. The reviewed Safety Report Action Sheet is placed in the respective study file; the action sheet is intended for internal use only and is not provided to the PI and/or study team. An email acknowledgement is sent to the appropriate study team members. Emails are also sent to request additional information pertinent to the review of the safety reports.
2) All subject pregnancies, subject withdrawals, clinical hold/study halt notifications, where the WRAIR IRB is Not the IRB of Record and they rely on another institution for IRB review, are submitted to the WRAIR IRB Administrator (or Designee), along with any action or notification from the reviewing IRB. The reviewed Safety Report Action Sheet is placed in the respective study file. An email acknowledgment is sent to the appropriate study team members.
3) All study deaths, where the WRAIR IRB is not the IRB of record and thereby rely on another institution for IRB review, are submitted to the WRAIR IRB Administrator (or Designee), along with any action from the reviewing IRB. The reviewed Safety Report Action Sheet is placed in the respective study file. An email acknowledgement is sent the appropriate study team members.
   a) Refer all SAEs/SUSARs and/or UADEs that also meet the definition of an UPIRTSO for review as per SOP UWS-HP-621, Deviation and Unanticipated Problem Reporting.
   b) The WRAIR IRB Administrator (or Designee) takes appropriate action(s) at his/her discretion:
      1. Request for more information;
      2. Acknowledge; no further action needed;
      3. Triage for review as an UPIRTSO;
      4. No action/file only.

c) The WRAIR IRB Administrator (or Designee) requests reporting, as applicable:
   1. Refer to the U.S. Army Medical Research and Development Command, Office of Research Protections, Human Research Protection Office (USAMRDC ORP HRPO) for review and approval; and/or
   2. Notifies the IO.

e. Communications to the Principal Investigator/Study Team

1) Safety reports are accepted by the IRB Chair (or Designee). The HSPB communicates this via an e-mail and may include a request for additional information or further action, as requested by the WRAIR IRB Chair (or Designee).
2) Safety reports, where the WRAIR IRB is not the IRB of record and they rely on another institutions' IRB for review, are acknowledged by the WRAIR IRB Administrator (or Designee) and the HSPB communicates this via an email and may include a request for additional information.
3) Safety reports may be submitted to the fully convened WRAIR IRB for review or for information only. As a result, the following action(s) may occur:
   a) If the full board review determines that the safety report warrants a modification of the protocol, consent form and/or other supporting documentation, an email ("Communication to PI" section from the respective IRB meeting minutes) is sent to the study team by HSPB. A more official communications path may also occur in which an official memorandum signed by the WRAIR IRB Chair (or Designee) is sent to the PI/Study Team.
   b) If the safety report is submitted to the fully convened WRAIR IRB for information only, no further action is required unless the IRB has comments or recommendations to provide to the study team; then a "Communication to PI" is sent by the HSPB to the PI/Study Team (refer to WRAIR SOP UWS-HP-628, Review of Human Subjects Research by the Fully Convened WRAIR Institutional Review Board).

f. Additional Reporting Requirements by the WRAIR IRB to the USAMRDC ORP HRPO

The following are reported by the WRAIR HSPB to the USAMRDC ORP HRPO, in accordance with the WRAIR SOP UWS-HP-636, Reporting Requirements to USAMRDC for Headquarters-Level Review:

1) All related SAEs/SUSARs;

2) All UADEs;
3) All deaths related to study participation;
4) All clinical hold/study halt notifications.

g. Reporting to Federal Regulatory Agencies

1) Department of Health and Human Services (HHS) Office of Human Research Protections (OHRP)

To be in compliance with the requirements of the Federal-wide Assurance (FWA) for studies that are funded by HHS, the WRAIR HSPB/IRB reports any internal SAEs/SUSARS or UADEs, (i.e. safety reports that occur at our sites) that meet the criteria as an UPIRTSO to the OHRP and to the supporting HHS agency head (or Designee). This report is submitted after WRAIR IRB review is completed and a determination as an UPIRTSO is made (as per SOP UWS-HP-621). A copy of this report is provided to the Sponsor and PI/Study Team.

2) Reporting to the U.S. FDA

For clinical trials that are funded by the Army Office of The Surgeon General (OTSG), The Surgeon General's Sponsor's Representative to the US FDA reports events in accordance with AR 40-7, 21 CFR 312.50, 21 CFR 812.150. For trials that are Sponsored by external entities (i.e., industry Sponsors), events are reported by the respective Sponsor.

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

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

Adverse Event	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related; symptoms or disease; abnormal lab findings, worsening of baseline condition; protocol-defined events. Grading AE seriousness (subjective and based on the investigator and subject's assessment) and severity (objective). The intensity of AE must be graded on a linear scale: Grade 1-mild AE; Grade 2-moderate AE; Grade 3-severe AE; Grade 4-life-threatening or disabling (hospitalization) AE; Grade 5-death related to AE. AEs of Grades 3-5 are generally considered SAEs. Grades 1-2

	can lead to SAEs if the frequency (number of occurrences) is higher than expected
Adverse Reaction	An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.
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.
Data and Safety Monitoring Board (DSMB)	A committee of experts, independent of the trial investigators, pharmaceutical Sponsor (if any), and funding agency, that periodically reviews the conduct and results of the trial to ensure the safety of participants and the validity and integrity of the data. Synonymous terms include Data Monitoring Committee (DMC) and Independent Data Monitoring Committee (IDMC).
DoD Research Monitor	Research monitors are physicians, dentists, psychologists, nurses, other healthcare providers, or other professionals capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Research monitors must be independent of the investigative team and possess sufficient educational and professional experience to serve as the subject/patient advocate. Research monitors may be identified by an investigator or appointed by an Institutional Review Board (IRB) or Institutional Official (IO). Responsibilities of Research Monitors are outlined in DoDI 3216.02.
Healthcare Provider	Licensed provider of care (such as, physician, nurse, physician's assistant, clinical psychologist, dentist, podiatrist, ophthalmologist, etc.)
HSPB	Human Subjects Protection Branch, WRAIR, provides administrative support to the WRAIR IRB.

Human Subject	A living individual about whom an investigator (whether professional or student) 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.
Human Subjects Research	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 obtains data through intervention or interaction with the individual, identifiable private information, or identifiable biospecimens.
Informed Consent	A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. The informed consent document (consent form) communicates the necessary information in a meaningful, understandable way. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the Sponsor, the institution or agents thereof from liability for negligence.
Life-threatening Adverse Event or Life-threatening Suspected Adverse Reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
Safety Monitoring Committee	A committee established by the Sponsor to review and evaluate the (unblinded) data from a study to assess safety risks to subjects. Typically, less formal than a DSMB/IDMC, the committee must contain at least one

	member who is independent from the investigator and Sponsor team.
Serious Adverse Event (OHRP)	OHRP defines serious adverse event as any adverse event that: 1) results in death; 2) is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3) results in inpatient hospitalization or prolongation of existing hospitalization; 4) results in a persistent or significant disability/incapacity; 5) results in a congenital anomaly/birth defect; or 6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).
Serious Adverse Event (SAE)	An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Serious and Unexpected Suspected Adverse Reaction (SUSAR)	Any suspected adverse reaction that is both serious and unexpected. Reporting of an adverse event as a suspected adverse reaction must occur only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

a. A singled occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
b. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
c. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group that in a concurrent or historical control group.

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 conduct an investigation 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.
Suspected Adverse Reaction (SAR)	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of FDA safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.
Unanticipated Problem	

Involving Risks to Subjects or Others (UPIRTSO)	Any incident, experience, or outcome that meets all of the following criteria: a. Unexpected (in terms or nature, severity, or frequency) given the approved research procedures and the subject population studied; b. Related or possibly related to a subject's participation in research; and c. Suggests that the research places subjects or others at greater risk of harm (physical, psychological, economic, or social harm) than was previously known or recognized.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unexpected Adverse Event (UAE) Or Unexpected Suspected Adverse Reaction (USAR)	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.
Research	A systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge (32 CFR 219.102d).

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 CFR 56.107 and 32 CFR 219.

7. References

Reference Number or Author	Document Title
32 Code of Federal Regulations (CFR) 219	Department of Defense, Protection of Human Subjects
45 CFR 46	Health and Human Services, Protection of Human Subjects
21 CFR 56	Institutional Review Boards
21 CFR 312	Investigational New Drug Application
21 CFR 312 and 320	Final Rule: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans, 29 September 2010
21 CFR 812	Investigational Device Exemptions
FDA Guidance	Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies 12 December 2012

FDA Guidance	Safety Assessment for IND Safety Reporting Guidance for Industry, December 2015
FDA Guidance	Adverse Event Reporting to IRBs — Improving Human Subject Protection Guidance for Clinical Investigators, Sponsors, and IRBs, January 2009
48 CFR 252.235-7004	Defense Federal Acquisition Regulation (48 CFR 252.235-7004) ("DFARS clause")
DoDI 3216.02	Department of Defense Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research (DODI 3216.02) (8 November 2011)
AR 40-7	Use of Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule 1 Controlled Substances
AR 70-25	Use Of Volunteers As Subjects of Research
10 USC 980	Title 10 of the United States Code, Section 980 (10 USC 980), Limitation on Use of Humans as Experimental Subjects
ICH – E6(R2)	Food and Drug Administration, Good Clinical Practice: Integrated Addendum to ICH E6(R1)
HHS OHRP	OHRP Guidance on the Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (2007)
USAMRDC Command Policy 2017-67	Event Reporting Requirements for Human Subjects for USAMRDC Conducted Research
Headquarters USAMRDC Memo	Delegation of The Surgeon General's Sponsor Representative to the US Food and Drug Administration (FDA) to the US Army

	Research and Development Command (USAMRDC) Principal Assistant for Acquisition (PAA) 27 March 2013
DASG-HRPO Department of the Army Office of the Surgeon General (OTSG); Memo	Waiver of DOD-Unique Human Subjects Protection Requirements for Certain Army- Supported, Non-DOD Conducted, Research Involving Human Subjects 24 JUL 2017
DASG-ZH Department of the Army Office of the Surgeon General (OTSG); Memo	Delegation to the Institutional Review Board (IRB) Chair of Waiver Authority of the Research Monitor (RM) Requirement for Greater Than Minimal Risk (GTMR) Army–Conducted and –Supported Human Subjects Research Where the Remaining Activities May be Reviewed by Expedited Procedure, 09 JUN 2017
NIH	Expedited Review of Human Subjects Research
WRAIR SOP UWS-HP-606	Non-Compliance Procedures
WRAIR SOP UWS-HP-618	Continuing Review and Continuation Determination
WRAIR SOP UWS-HP-636	Reporting Requirements to USAMRDC ORP HRPO for Headquarters-level Review and to AHRPO
WRAIR SOP UWS-HP-621	Deviation and Unanticipated Problem Reporting
WRAIR SOP UWS-HP-628	Review of Human Subjects Research by the Fully Convened WRAIR Institutional Review Board

8. **Forms and Appendices**

Form or Number	Title
Appendix A	WRAIR IRB Safety Report Action Sheet
Appendix D from UWS-HP-621	Deviation and Unanticipated Problem Reporting

9. **Document Revision History**

Version Number	Brief Description of Changes	Effective Date
.00	Original SOP	07 May 2007
.01	Biennial review, including organization name updates and references to current policies and procedures, and updating the SOP title for	Revisions (in draft only)
.02	1. Align responsibilities and activities with current DOD regulations 2. Provide guidance for the principal investigators 3. Clarify procedures for safety reviews, monitoring plans, and reports.	18 August 2010
.03	1. Add new requirements and definitions with current FDA safety reporting guidance. 2. Editorial revisions to update Branch names, references, etc.	02 MAY 2018
.04	Update the SOP to clarify the role of the WRAIR IRB Administrator when reviewing safety reports for studies where the WRAIR IRB is not the IRB of record and they are relying on another institution's IRB. Other revisions to incorporate updated guidance, policies, regulations, and minor editorial clarifications.	