



**WALTER REED ARMY INSTITUTE OF RESEARCH**  
 Division of Human Subjects Protection  
 Standard Operating Procedure



SOP Title	<b>Safety Reporting for Clinical Trials</b>	SOP No.	<b>UWZ-C-619</b>
		Revision	<b>.02</b>
Effective Date	AUG 18 2010	Page	1 of 17

**Signatures and Dates:**

Authors: {

For signatures, please see original in the  
 Division of Human Subjects Protection

QA Review: ←

Approving  
 Authority:

**Review/Approval for unchanged documents**

	Author/Date	QA Review/Date	Approving Authority/Date
1			
2			
3			



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## 1. Purpose/Applicability

This standard operating procedure (SOP) outlines the process for documentation and review of safety reports and exceptions to the safety monitoring plan received by the Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) from investigators, medical monitors, Sponsors, or data and safety monitoring boards /safety monitoring committees (DSMB/SMC).

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

A safety report includes any of the following serious adverse event (SAE) reports (related & unexpected): an initial, follow-up, final, Medical Monitor, an unanticipated adverse device effect and summary from a DSMB/SMC or Sponsor's safety reports submitted to the U.S. Food and Drug Administration (FDA).

This SOP applies to the Division of Human Subjects Protection (DHSP) staff, the WRAIR IRB, investigators, medical monitors, and WRAIR Commander (Institutional Official; IO).

## 2. Responsibilities

- a. **DHSP Human Subject Protection Scientist (HSPS)** is the DHSP staff member assigned to review the protocol and manage the IRB documentation for that study
- b. **WRAIR IRB Chair or Designee** reviews safety reports and exceptions to the safety monitoring plan as outlined below, and takes appropriate action
- c. **WRAIR IRB** ensures an adequate safety plan of all protocols approved by the IRB, and reviews safety reports as referred from the WRAIR IRB Chair or designee, and takes appropriate action for any issues cited in the report to ensure the safety of study participants
- d. **Investigators** report as per required
- e. **Medical Monitors** (and their designated alternates) assist the IRB with issues of individual subject/patient management and safety.
- f. **WRAIR Commander (IO)** approves exceptions to the safety monitoring plan



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### 3. Investigator Guidance

The Principal Investigator (PI) is advised to:

- a. Ensure that a DSMB/SMC (if applicable) is established when submitting protocols to the WRAIR IRB and ensure that a safety monitoring plan and DSMB/SMC charter is included with the initial submission to the WRAIR IRB for review and approval.
- b. Ensure that a medical monitor and/or alternate medical monitor is/are assigned in accordance with the requirements of the Department of Defense (DoD) Directive 3216.02 for studies anticipated to be greater than minimal risk and supported by the DoD (funding, resources, personnel, etc.).
- c. Promptly submit any SAEs, unexpected AEs, unanticipated problems, and unanticipated adverse device effects, as applicable, to the WRAIR IRB via the WRAIR DHSP, including associated medical monitor reports, and safety summaries from the DSMB/SMC during the course of the trial and at the time of continuing review.
- d. Investigators should immediately report by telephone or email SAEs (per DHSP SOP UWZ-C-611.01 Prompt Reporting to the WRAIR IRB) and promptly report (within 48 hours) AEs meeting the following criteria when s/he becomes aware of the event and then must follow-up in writing within 10 working days from knowledge of the event:
  - i. **SERIOUS** (i.e., death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect [21 CFR 312.32(a)]), and
  - ii. **UNANTICIPATED** (An unanticipated event is any adverse experience where the nature, severity or frequency is not identified in the investigator brochure or described in the protocol. Events which are already cited in the investigator brochure or protocol are not unanticipated and do not have to be reported to the WRAIR IRB, except in the continuing review report), and
  - iii. **RELATED** to the study design, procedures, or drug/device (possibly, probably or definitely related, or undetermined/unknown). If the adverse experience/event is clearly not related to the study drug, device, procedures, or washout process, it would not represent a risk to other subjects in the research and, therefore, does not have to be reported to the WRAIR IRB.



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Failure to report SAEs/AEs meeting any of the above-described criteria is considered non-compliance (refer to WRAIR SOP, Non-Compliance Procedures, UWZ-C-606.01).

Reporting:

- e. (Drugs, Biologics, Devices) Investigators should report promptly by telephone or email (within 48 hours) unanticipated problems, when s/he becomes aware of the event and then must follow-up in writing within 10 working days from knowledge of the event.

(Devices) Investigators shall report by telephone or email (within 48 hours) unanticipated adverse device effects, when s/he becomes aware of the event and then must follow-up in writing within 10 working days from knowledge of the event.

Failure to report the above is considered non-compliance (refer to WRAIR SOP, Non-Compliance Procedures, UWZ-C-606.01).

- f. Submit any SAEs, unexpected AEs, unanticipated problems, unanticipated adverse device effects, as applicable, to the Sponsor in accordance with the Sponsor's requirements. These requirements are in addition to reporting to the WRAIR IRB.
- g. 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 a study subjects. If immediate action is taken, this must be reported to the IRB/DHSP within 24 hours.
- h. Respond to requests for documentation and information from the WRAIR IRB and WRAIR DHSP.
- i. Maintain correspondence with the reviewing IRBs, Sponsor, and regulatory authorities, as appropriate.



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**4. Materials and Equipment**

Not applicable

**5. Procedures**

**a. Prior to Protocol Approval**

- 1) Before research is approved, the WRAIR IRB gives appropriate consideration to the spectrum of adverse events 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, and the Board may not have the expertise to serve as a safety monitoring board. The IRB does have a duty to ensure that the Sponsor's safety officer, the designated medical monitor (and alternate medical monitor as appropriate), and/or the DSMB/SMC assigned to safety oversight of a particular clinical trial are impartial and qualified to perform its safety assessment. A list of members of safety committees and their qualifications is to be provided to the WRAIR IRB as part of the protocol review.
  - a) All DSMBs or SMCs should have at least one impartial member. It is recommended that the DoD Medical Monitor serves as a member of the DSMB/SMC.
  
  - b) Conflict of interest statements for all safety committee members should be maintained in the Sponsor's regulatory file (Investigators regulatory file for Investigator-initiated research), and be available to the IRB upon request.
  
- 3) In accordance with the DoD Directive (DoDD) 3216.02, all studies determined to be greater than minimal risk [as defined by 32 CFR 219.102(i)] require an independent DoD medical monitor. (Note: At the discretion of the IRB, a medical monitor may also be assigned for minimal risk studies.) The medical monitor is assigned to discuss research progress with the PI, interview subjects, consult on individual cases, or evaluate adverse experience/event reports on behalf of the IRB. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect



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the safety and well-being of research subjects until the IRB can assess the medical monitor's report. The WRAIR IRB is responsible for ensuring that the individual is appropriately qualified to serve in this role. Medical Monitors are required to review all unanticipated problems involving risks to subjects or others, serious adverse event reports, unanticipated adverse device effects, and all subject deaths, and provide an unbiased written report of the event promptly to the WRAIR IRB by phone (301) 319-9940, or by email ([WRAIRDHSP@amedd.army.mil](mailto:WRAIRDHSP@amedd.army.mil)), or by facsimile (301) 319-9961. The DoD Medical Monitor or their approved alternate will then submit written reports within 10 working days to the WRAIR IRB.

**b. Review of Safety Reports by the WRAIR IRB**

- 1) Safety reports are initially received by the DHSP Human Subjects Protection Scientist (HSPS) for that study. The HSPS provides the safety report, including additional documentation (i.e., Sponsor's opinion and the medical monitor's report) and the corresponding Safety Report Action Sheet (see Appendix A) to the WRAIR IRB Chair (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.
- 2) A health care provider IRB member must review all safety reports.
- 3) All study deaths should be reported to the WRAIR IRB, regardless of relatedness. The IRB Chair (or designee) will determine which reports of subject deaths should be forwarded to the full board.
- 4) The WRAIR IRB Chair (or designee) takes appropriate action(s) at his/her discretion:
  - a) Request for more information;
  - b) Refer to full WRAIR IRB for review;
  - c) Refer to the full WRAIR IRB for information only;
  - d) Approve or Accept; no further action required;
  - e) Approve or Accept; with minor corrections to the safety reports;
  - f) Approve or Accept: requires modification to protocol-related documents;



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- g) Refer to the U.S. Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protections Office (USAMRMC ORP HRPO) for review and approval;
- h) The IO reports to the U.S. Department of Health and Human Services, Office of Human Research Protections (DHHS OHRP);
- i) No action/file only

(Note: If the WRAIR IRB is not the IRB of record and is maintaining an IRB shadow file only; this may be signed by DHSP, not the IRB Chair).

5) SAE, unexpected adverse experience/event, unanticipated adverse device effect reports, are paired up by the HSPS with the medical monitor report and any subsequent follow-up and final reports to provide additional context for final disposition.

6) The following safety reports require review by a fully convened WRAIR IRB:

a) SAEs that are unanticipated, serious, & related to an investigational product and determined by the WRAIR IRB Chair to require full board review. All other WRAIR Site SAEs (expected or unexpected) that are related to an investigational product will be provided to the fully convened WRAIR IRB for information purposes only;

b) All unanticipated adverse device effects;

c) All unanticipated problems that otherwise increase risk to subjects or others; and,

d) All deaths.

7) All summary safety reports from the Sponsor or Sponsor-designated DSMB/SMC are initially reviewed by the WRAIR Chair (or designee), and then provided to all IRB members for review or information only.

**Review of Exceptions to the Safety Monitoring Plan 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 DHSP HSPS for that study. The



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DHSP 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 member.

- 2) The WRAIR IRB Chair (or designee) may request additional information from the medical monitor, SMC/DSMB, and others, where appropriate, before providing a recommendation of 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 will be provided in writing.

**c. Response to the Principal Investigator/Study Team**

- 1) Safety reports are acknowledged by the DHSP via an e-mail and may include a request for additional information or further action, as acted upon by the WRAIR IRB Chair (or designee).
- 2) Safety reports may be submitted to the WRAIR IRB for full board review or information only. As a result, the following action(s) may occur:

If the full board review determines that the safety report warrants a modification of the protocol &/or supporting documentation, an email ("Communication to PI" section from the respective IRB meeting) is sent to the study team. A more official path may occur in which an official memorandum signed by the WRAIR IRB Chair (or designee) is sent to the PI/Study Team.

If information only, a "Communication to PI" with no actions required, will be sent.

(Refer to WRAIR SOP, WRAIR IRB Meeting Minutes, UWZ-C-625.01).

- 3) All exceptions to the safety monitoring plan are acknowledged and recommended for approval by written memorandum from the WRAIR IRB Chair (or designee) and provided to the WRAIR Commander (IO) for implementation approval.

**d. Continuing Review of Protocol**

- 1) The WRAIR IRB reviews the safety data as part of the continuing review to determine if any new information has emerged during the current review period



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that could alter the study's risk:benefit assessment. Safety information reviewed includes, but is not limited to, interval summary of all SAEs, a cumulative summary of drug-related AEs, current Investigator's Brochure (with version number and date) and any new publications that may include new safety data. Additionally, all safety reports provided to the IRB since the most recent continuing review are listed as an appendix to the report (Refer to WRAIR SOP, Continuing Review and Continuation Determination, UWZ-C-618.01).

- 2) The IRB confirms that any provisions for monitoring study data for safety of subjects have been implemented and are working as intended.

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

The following are reported by the WRAIR DHSP to the USAMRMC ORP HRPO, in accordance with the WRAIR SOP, Reporting Requirements to USAMRMC for Headquarters-Level Review, UWZ-C-636:

1. All serious adverse events related to the investigational product;
2. All unanticipated adverse device effects;
3. Unanticipated problems that increase risk to subjects or others; and
4. All deaths related to study participation.

**g. Reporting to DHHS 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 the DHHS, the WRAIR DHSP/IRB reports any internal adverse events that are unanticipated to the OHRP and to the supporting HHS agency head (or designee). This report is submitted after WRAIR IRB review is completed. A copy of this report is provided to the Sponsor and PI.

**h. Reporting to the U.S. FDA**

For clinical trials that are Sponsored by the Army OTSG, the U.S. Army Medical Materiel Development Activity (USAMMDA) reports events in accordance with AR 40-7 and 21 CFR 312.5. For trials that are sponsored by external entities (i.e., industry sponsors), events are reported by the respective Sponsor.



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**6) Explanation of Abbreviations and Terms**

**Adverse Event** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

**Clinical Trials** Any investigation in human subjects intended to discover or to verify the clinical pharmacological, pharmacokinetic, and/or other pharmacodynamic effects of an investigational agent, and/or to identify any adverse reactions to an investigational agent to assess the agent's safety and efficacy.

**Data & Safety Monitoring Board (DSMB)** An independent, chartered committee established by the sponsor to assess, at defined intervals, the ongoing scientific and ethical integrity of a study by reviewing and evaluating (unblinded) data and reports. The DSMB makes non-binding reports to the sponsor regarding study modification, suspension or termination. Synonymous terms include Data Monitoring Committee (DMC) and Independent Data Monitoring Committee (IDMC).

**Healthcare Provider** Licensed provider of care (such as, physician, nurse, physician's assistant, clinical psychologist, dentist, podiatrist, optometrist, etc.)

**Medical Monitor** An independent medical monitor fulfills a unique DoD requirement in human subjects protection. Medical monitors shall be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual volunteer/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and



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professional experience to serve as the volunteer/patient advocate. Industry-sponsor medical monitors (i.e., the Sponsor's medical expert) generally do not meet the intent of DoD Directive.

**Related**

An event related to the study design, procedures, or drug/device (possibly, probably or definitely related, or unknown). If the event is clearly not related to the study drug, device, procedures, or washout process, it would not represent a risk to other subjects in the research and, therefore, does not have to be reported to the WRAIR IRB.

**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, the committee must contain at least one member who is independent from the investigator and sponsor team.

**Serious Adverse Experience/Event (FDA)**

Any adverse experience/event temporally associated with the subject's participation in research that meets any of the following criteria: 1) results in death; 2) is life-threatening (*Life-threatening adverse drug experience* is defined as any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.); 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in persistent or significant disability or incapacity (*Disability*: A substantial disruption of a person's ability to conduct normal life functions.); 5) results in congenital anomaly/birth defect (in the offspring of a subject); 6) important medical adverse events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, **based upon appropriate**



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**medical judgment**, they may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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 (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).

**Sponsor**

An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

**Unanticipated Problem**

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;



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- 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** 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** Any adverse event occurring in one or more subjects in a research protocol, for which the nature, severity or frequency of the adverse event is not consistent with: 1) The known or foreseeable risk of adverse events associated with procedures that are described in protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or 2) The expected natural progression of any underlying disease or condition of the subject that places the subject at a greater risk of physical harm that was previously known or recognized.



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**7) References**

<b>Reference Number or Authors</b>	<b>Document Title</b>
32 CFR 219	Protection of Human Subjects
21 CFR 56	Institutional Review Boards
21 CFR 312	Investigational New Drug Application
21 CFR 812	Investigational Device Exemptions
45 CFR 46	Protection of Human Subjects
DoDD 3216.02	Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research
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
ICH – E6	International Conference of Harmonization. (1997). Good Clinical Practice: Consolidated Guidance (ICH-E6). Section 3.
DHHS OHRP	OHRP Guidance on the Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (2007)
MRMC	HSRRB Policy Memorandum 02-01. Reporting to the HSRRB Unanticipated Problems Involving Risks to Subjects or Others
NIH	Further Guidance On A Data And Safety Monitoring For Phase I And Phase II Trials (2000)
FDA	Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting – Improving Human Subject Protection (January 2009)



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WRAIR SOP UWZ-C-618	<i>Continuing Review and Continuation Determination</i>
WRAIR SOP UWZ-C-625	<i>WRAIR IRB Meeting Minutes</i>
WRAIR SOP UWZ-C-636	<i>Reporting Requirements to USAMRMC for Headquarters-level Review</i>



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**8) Forms and Appendices**

Form or Number	Title
Appendix A	WRAIR IRB Safety Report Action Sheet

**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 clarity.	Revisions (in draft only)
.02	<ol style="list-style-type: none"> <li>1. A-line responsibilities and activities with current DOD regulations</li> <li>2. Provide guidance for the principal investigators</li> <li>3. Clarify procedures for safety reviews, monitoring plans, and reports.</li> </ol>	<b>AUG 18 2010</b>



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**APPENDIX A**

**WRAIR IRB Safety Report Action Sheet**

WRAIR Protocol #: \_\_\_\_\_ DHSP POC: \_\_\_\_\_

PI: \_\_\_\_\_ Sponsor: \_\_\_\_\_

Date of Event: \_\_\_\_\_ Subject Number: \_\_\_\_\_/Site: \_\_\_\_\_

Date Received: \_\_\_\_\_

Date Submitted to Chair for Review: \_\_\_\_\_ SAE/UAE/UADE/UAP #: \_\_\_\_\_

**Documentation Provided (check all that apply):**

- Bundled SAE Package
- Initial SAE/Unexpected Event Report
- Unanticipated problem
- Follow-up SAE/Unexpected Event Report (# \_\_\_\_\_)
- Medical Monitor's Report (date \_\_\_\_\_)
- Safety Summary from Safety Committee or DSMB
- Safety Letter from Sponsor/MedWatch Report
- Other

**Action Taken (check all that apply):**

- Request for More Information: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



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- Refer to Full WRAIR IRB for Review  
OR For Information Only (circle one)
- Approved or Accepted; no further action required
- Approved or Accepted; with minor corrections to the reports
- Approved or Accepted; requires modification to protocol-related documents
- Referred to USAMRMC ORP HRPO
- Submit to OHRP
- No action; file only

Comments:

Signature: \_\_\_\_\_ Date: \_\_\_\_\_