Standard Operating Procedure
Walter Reed Army Institute of Research

SOP Title	**Deviation and Unanticipated Problem Reporting**	SOP No.	**UWS-HP-621**
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Signatures and Dates:

Author:

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) outlines the process for documentation and review of deviations and unanticipated problems. Adverse events occurring on non-product studies that are considered unexpected in nature, are to be reported as unanticipated problems under this SOP. Any Serious Adverse Event (SAE), Serious and Unexpected Suspected Adverse Reaction (SUSAR), and Unanticipated Adverse Device Effect (UADE) reported under SOP UWS-HP-619, that are considered unexpected in nature are also to be reported as unanticipated problems under this SOP and considered as potential Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs). This SOP applies to Walter Reed Army Institute of Research (WRAIR) Human Subjects Protection Branch (HSPB) staff, the WRAIR Institutional Review Board (IRB) Chair or designee, the WRAIR IRB members, and the WRAIR Institutional Official (IO). Investigator guidance is also included herein.

NOTE: Please refer to the Office of Human Research Protections, Unanticipated Problems Involving Risks & Adverse Events Guidance, for more detail on when adverse events are to be reported as unanticipated problems.

2. Responsibilities

a. WRAIR HSPB staff are responsible for:

1) Receiving telephone, email, facsimile, and written reports for both deviations and unanticipated problems.

2) Triaging the deviations and/or unanticipated problems, requesting additional information as necessary, determining if it meets the criteria for immediate reporting, and submitting to the WRAIR IRB Chair and/or WRAIR IRB or IRB Administrator, as appropriate, for review.

3) Sending the WRAIR IRB communications to the PI regarding the review of the deviations and unanticipated problems.

4) Archiving all immediately reportable deviation and unanticipated problem reports in the protocol regulatory file.

5) On behalf of the IO, reporting serious or continuing noncompliance (as per UWS-HP-606) and UPIRTSOs to the U.S. Army Medical Research and Development Command, Office of Human and Animal Research Oversight, Office of Human Research Oversight (USAMRDC OHARO OHRO), as per USAMRDC Policy 17 and the Director, Office for Human Research Protection (DOHRP) in accordance with DoDI 3216.02 § 3.1.h.

b. For studies reviewed by the WRAIR IRB, the WRAIR IRB Chair or designee is responsible for:

1) Initial IRB review and assessment of potential major deviations and unanticipated problems that are potential UPIRTSOs.

2) Seeking expert guidance from a healthcare provider IRB member for any medical issues arising from the deviations and unanticipated problems.

3) Recommending initial action on behalf of the IRB.

4) Referring all potential major deviations and unanticipated problems considered to be potential UPIRTSOs to the fully convened WRAIR IRB, as appropriate, for review and final determination. All major deviations will be submitted for consideration as serious and/or continuing non-compliance.

c. For studies reviewed by the WRAIR IRB, the WRAIR IRB is responsible for:

1) Reviewing and assessing the potential major deviations and unanticipated problems considered to be potential UPIRTSOs, and the study team's corrective action plan, as appropriate.

2) Determining whether the potential major deviations meet the criteria for a major deviation.

3) Determining whether unanticipated problems considered to be potential UPIRTSOs meet the reporting requirements as outlined in the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

4) Determining whether the major deviation resulted in serious and/or continuing non-compliance by the investigator as per SOP UWS-HP-606, Non-Compliance Procedures.

5) Recommend reporting to the IO, OHARO, OHRP, funders, partners, and the relevant federal department or agency head.

d. For studies where the WRAIR is relying on another institution for IRB review, the WRAIR IRB Administrator or designee is responsible for:

1) Review and assessment of potential major deviations and unanticipated problems that are potential UPIRTSOs.

2) Requesting documentation of IRB determinations from the WRAIR POC for major deviations and potential UPIRTSOs.

3) Requesting reporting to the IO, OHARO, OHRP, funders, partners, and the relevant federal department or agency head, as appropriate.

e. For studies reviewed by the WRAIR IRB, the WRAIR Institutional Official (IO):

1) Reviews and approves/disapproves the disposition of major deviations and/or UPIRTSOs as summarized in the IRB minutes. Provides input if there are additional actions that need to be taken, however, it is noted that the IO cannot downgrade what has been requested by the IRB.

2) Under circumstances involving serious and/or continuing non-compliance, the IO may review the major deviation prior to issuance of the IRB minutes, per the SOP UWS-HP-606, Non-Compliance Procedures.

3) Ensures action is taken if investigators do not adhere to the reporting requirements.

4) Requests HSPB to report serious and/or continuing noncompliance and UPIRTSOs to USAMRDC OHARO OHRO as per USAMRDC Policy 17, to the Director, Office for Human Research Protection (DOHRP) in accordance with DoDI 3216.02 § 3.1.h.and to the relevant federal department, agency head, or others on his/her behalf.

3. **Investigator Guidance:**

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

1) Submit protocol deviation(s) as follows:

a. Major deviations must be promptly reported (within 48 hours upon becoming aware of the event) to the HSPB by email or facsimile (using the Deviation/Unanticipated Problem Report Form, Appendix A, or a memorandum with similar content) and recorded in the study deviation log (refer to Appendix C). Major deviations may be initially reported by phone as well. The PI is responsible for making the initial determination; however, guidance should be obtained from the HSPB office, if needed. A written report must be subsequently submitted to the HSPB within 10 working days of knowledge of the event. Follow-up reports may also be appropriate as more information is gathered.

Major deviations may include, but are not limited to:
i. Written consent not obtained or consent form missing;
ii. Therapy or protocol interventions initiated prior to consent;
iii. Inclusion or exclusion criteria deviation;
iv. Delayed reporting of Serious Adverse Events (SAEs), unexpected adverse events, or unanticipated problems;
v. Incorrect dosing of any study product.

b. Minor deviations (deviations not considered to be major deviations) should be reported in the deviation log (refer to Appendix C) and reported to the IRB as part of the continuing review (see SOP UWS-HP-618, Continuing Review and Continuation Determination and SOP UWS-HP-638, Progress Reports and Continuation Determination).

Minor deviations may include, but are not limited to:

i. Study procedure conducted out of sequence;
ii. Copy of the Consent form not given to the person signing the form;
iii. Subject's visit was outside of study window (less than 2 days);
iv. Over-enrollment (depending on the nature of the study and the number enrolled);
v. Failure to perform a required lab test and this lab test is not known to be adversely affected by the study intervention;
vi. Failure of subject to return unused study drug.

Note: Any of the above listed deviations may be assessed as major deviations depending on the severity and frequency.

2) Submit unanticipated problems that may be potential UPIRTSOs as follows:

a. The WRAIR IRB/HSPB requires prompt reporting of potential UPIRTSOs (using the Deviation/Unanticipated Problem Report Form, Appendix A or a comparable form) to the HSPB (within 48 hours) upon becoming aware of the event by telephone, facsimile, or email, and recording it in the study unanticipated problem log (refer to Appendix C). A written report is required to be submitted by the PI to the HSPB within 10 working days of knowledge of the event.

b. All other unanticipated problems should be included in the deviation/unanticipated problem log and reported to the HSPB/IRB as part of the protocol continuing review, as per the SOP UWS-HP-618, Continuing Review and Continuation

Determinations and SOP UWS-HP-638, Progress Reports and Continuation Determination.

c. Any unanticipated problems or protocol deviations identified by a Sponsor's Monitor and reported to the WRAIR PI/POC must be reported following the time frames described above.

3) Respond to requests made by the HSPB, WRAIR IRB and/or WRAIR IRB Chair/ Designee or IRB Administrator regarding the deviation(s) or unanticipated problems, no later than five (5) business days from the receipt of the request, unless either waived or modified by the Director, HSPB, or the WRAIR IRB Chair or designees. Failure to respond to a request may result in the initiation of non-compliance procedures as per the SOP UWS-HP-606, Non-Compliance Procedures.

4) Adhere to the Sponsor's reporting requirements and timelines in addition to those of other overseeing IRBs/Ethical Review Committees, and the WRAIR IRB.

4. **Materials and Equipment**

Not Applicable

5. **Procedures**

a. HSPB staff:

1) Upon notification of a deviation or unanticipated problem via phone, email, facsimile, or written memorandum: make an initial assessment to determine if it meets the prompt reporting requirements and/or to determine if any harm to study participant(s) has/have or may have occurred. If the deviation or unanticipated problem meets either of these requirements, then immediately report it to the IRB Chair/Designee or IRB Administrator for review, as appropriate.

2) If the deviation or unanticipated problem does not meet the immediate reporting criteria, then send an email acknowledgement to the study team that acknowledges receipt of the report and notify them that the report should be summarized in the next continuing review/progress report. Include a copy of the deviation or unanticipated problem report in the next electronic continuing review/progress report folder for the HSPB continuing review/progress report POC.

3) Assist the PI/POC, as needed, to complete the Protocol Deviation/Unanticipated Problem Report Form (Appendix A) for the written report.

4) Assess the deviation/unanticipated problem and request additional information from the PI/POC, as necessary to make a determination about the reporting requirements for the report.

5) Upon receipt of the completed Protocol Deviation Report/ Unanticipated Problem Form, attach the Protocol Deviation/ Unanticipated Problem Report Action Sheet (Appendix B) and any other pertinent correspondence, and provide to the WRAIR IRB Chair/Designee or IRB Administrative Director, as appropriate, for review.

6) For studies reviewed by the WRAIR IRB: If the WRAIR IRB Chair or designee has determined that the deviation is classified as a major deviation or that the unanticipated problem is potentially an UPIRTSO, place the report on the next fully convened WRAIR IRB meeting for review and determination, as appropriate.

7) For studies where the WRAIR IRB is relying on another institution for ethical oversight: If the WRAIR IRB Administrator or designee has determined that the deviation is classified as a major deviation or that the unanticipated problem is potentially an UPIRTSO, request the documentation of IRB review and determination from the reviewing IRB.

8) Relay to the PI any actions required following deliberations and determinations from the IRB Chair or designee and/or the fully convened IRB, or IRB Administrator, as appropriate.

9) Archive a copy of the Protocol Deviation/Unanticipated Problem Report Form(s), the Protocol Deviation/ Unanticipated Problem Report Action Sheet(s), and copies of all communications and records relating to the event and its outcome.

10) For all UPIRTSOs, as determined by the IRB, notify the WRAIR IO and USAMRDC OHARO OHRO following the IRB meeting or upon receiving the documentation from the reviewing IRB.

11) On behalf of the IO notify the USAMRDC OHARO OHRO of all UPIRTSOs determined by the WRAIR or reviewing IRB to meet the reporting requirements as outlined in the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

12) On behalf of the IO notify the USAMRDC OHARO OHRO, as per USAMRDC Policy 17, of any major deviations that are determined to be in serious and/or continuing noncompliance as per WRAIR SOP UWS-HP-606.

13) On behalf of the IO notify the Director, DOHRP through the COHRP within 5 business days of the UPIRTSO or serious and/or continuing non-compliance report's completion in accordance with DoDI 3216.02 § 3.1.h.

b. For studies reviewed by the WRAIR IRB, the WRAIR IRB Chair or designee:

1) Upon notification of a potential major deviation or unanticipated problem considered to be a potential UPIRTSO review the deviation/unanticipated problem as soon as possible and obtain further information from the PI, as needed.

2) Make one of the following determinations (as listed on the Protocol Deviation/Unanticipated Problem Report Action Sheet):

(a) Request more information and specify in the blank space provided on the form, what additional information should be provided to make an accurate assessment;

(b) Accept the deviation/unanticipated problem report or summary as written, with no further action required (in other words the deviation did not result in serious or continuing noncompliance or the unanticipated problem is not considered a potential UPIRTSO);

(c) Accept the deviation/unanticipated problem report, with full approval contingent upon modification to the protocol/protocol-related documents and/or the submission of a corrective action plan;

(d) Refer to full WRAIR IRB for further review and determination as to whether the report is a major deviation that resulted in serious or continuing noncompliance or an unanticipated problem that is a potential UPIRTSO;

(e) Accept the deviation/unanticipated problem report and refer to the full WRAIR IRB for information only;

(f) The WRAIR IRB Chair or designee can request that the HSPB Staff or WRAIR IRB Administrative Director make any of the required notifications specified in section 5.a.10 and 5.a.11 of this document.

3) For studies reviewed by the WRAIR IRB, the WRAIR IRB reviews the potential major deviation (resulting in either potentially serious or continuing noncompliance

with the study) or unanticipated problem considered to be a potential UPIRTSO, and associated actions as forwarded by the IRB Chair and/or designee using the form UWS-HP-621 Appendix D and either:

(a) Accepts the potential major deviation or potential unanticipated problem considered

to be a potential UPIRTSO or summary as written;

(b) Request the PI to submit more information or a follow-up report to include a plan of action, as appropriate;

(c) Make a determination as to whether or not the deviation is major or the unanticipated problem is an UPIRTSO (according to the definitions); determine if the major deviation resulted in serious and/or continuing non-compliance by an investigator in accordance with the SOP UWS-HP-606, Non-Compliance Procedures; and make a recommendation for course of action. Non-compliance determinations will be forwarded to the WRAIR IO for consideration in accordance with the SOP UWS-HP-606, Non-Compliance Procedures;

(d) Specify whether any or all of the following parties should be notified of the UPIRTSO and/or serious and/or continuing non-compliance arising from the major deviation: WRAIR IO, USAMRDC OHARO OHRO, and/or relevant federal department or agency head.

c. For studies where the WRAIR is relying on another institution for IRB review, the IRB Administrator or designee:

1) Upon notification of a potential major deviation or unanticipated problem considered to be a potential UPIRTSO review the deviation/unanticipated problem as soon as possible and obtain further information from the PI/POC, as needed.

2) Request the documentation of IRB review from the reviewing IRB.

3) Make one of the following determinations (as listed on the Protocol Deviation/Unanticipated Problem Report Action Sheet):

(a) Request more information and specify in the blank space provided on the form, what additional information should be provided to make an accurate assessment;

(b) Acknowledge the deviation/unanticipated problem report or summary as written, with no further action required (in other words the deviation did not result in serious or continuing noncompliance or the unanticipated problem is not considered a potential UPIRTSO);

(c) Acknowledge the deviation/unanticipated problem report, with IRB approval from the reviewing IRB.

4) Report serious and/or continuing noncompliance and UPIRTSOs to USAMRDC OHARO OHRO and/or the relevant federal department or agency head on behalf of the WRAIR IO.

d. For studies reviewed by the WRAIR IRB, the WRAIR IO:

1) Approves/Disapproves the disposition of the major deviation/UPIRTSO and the action taken by the IRB.

2) When appropriate, reviews and approves/disapproves corrective action plans.

3) Requests that the HSPB report serious and/or continuing noncompliance and UPIRTSOs to USAMRDC OHARO OHRO and/or the relevant federal department or agency head on their behalf.

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 Author	Document Title
21 CFR 56	Code of Federal Regulations, Institutional Review Boards
32 CFR 219	Code of Federal Regulations, Protection of Human Subjects
45 CFR 46	Code of Federal Regulations, Protection of Human Subjects
DoDI 3216.02	Department of Defense Instruction 3216.02
OHRP Guidance on UPIRTSOs	Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 15 January 2007
WRAIR HRPP	WRAIR Human Research Protection Program (HRPP)
WRAIR IRB Charter	WRAIR Institutional Review Board (IRB) Charter
SOP UWS-HP-606	Non-Compliance Procedures
SOP UWS-HP-618	Continuing Review and Continuation Determination
SOP UWS-HP-619	Safety Reporting for Clinical Trials

USAMRDC Policy 17	Event Reporting Requirements for Human Subjects Research Conducted by the USAMRDC

8. Appendices and Attachments

Appendix or Attachment Number	**Title**
UWS-HP-621 Appendix A	HSPB Protocol Deviation/Unanticipated Problem Report Form
UWS-HP-621 Appendix B	HSPB Protocol Deviation/Unanticipated Problem Report Action Sheet
UWS-HP-621 Appendix C	HSPB Protocol Deviation/Unanticipated Problem Log
UWS-HP-621 Appendix D	Fully Convened WRAIR IRB Review of Deviations and Unanticipated Problems

9. Document Revision History

Version Number	Brief Description of Changes	Effective Date
.00	Original document	17 Nov 2008
.01	Updated with unanticipated problems and reporting requirements due to rescinding both the WRAIR SOP, Ensuring Prompt Reporting to the HURC (UWZ-C-611) and the Guidance on Reporting Deviations to the WRAIR Division of Human Subjects Protection.	21 Mar 2011
.02	Clarified the reporting requirements for noncompliance and UPIRTSOs and added the reference to the Command Policy 2011-67.	02 Nov 2011

.03	Updated the SOP to clarify the responsibilities of the HSPB, IRB Chair/Designee, and WRAIR IRB in triage and review of deviations and unanticipated problems, as well as, include recommendations from AHRPO	03 Mar 2023
.04	Reformatted using new WRAIR SOP template and other minor administrative and editorial changes.	07 August 2024