Procedure Title: Required Reporting: Unanticipated Problems and Adverse Events

Associated Policy:	Human Research Protection Policy (OSA Policy 1.0)		
Responsible Unit:	Office of Scholarly Activity		
Created:	06/03/2020	**Executive Lead:**	Chief Research Officer
Effective:	06/30/2020	**Revision History:**	.00 – 06-03-2020; .01 – 1-25-2023; .02 – 4-2-2024; .03 – 8-26-2024
Approved by:	Institutional Review Board		
Procedure Number:	134.03		
Key Words:	Adverse Event, Corrective and Preventative Action Plan (CAPA), Reportable Event, Serious Adverse Event, Unanticipated Problems		
Purpose:	To meet the responsibilities for protecting human subjects as issued by the Office for Human Research Protections (OHRP) requirement for individuals involved in the conduct or review of human subjects research at institutions holding OHRP-approved Federal Wide Assurances (FWAs)		

Process:
This SOP serves to inform all agents, offices, departments, and affiliate sites of PNWU regarding reportable events in human subjects research.

This SOP must be used as a guide in parallel with OSA Policy 1.0 to comply with proper reporting of unanticipated problems involving risk to subjects or others. SOPs are not intended to supersede existing institutional policies, and local, state, and federal laws and regulations.

General Information and Key Definitions:

Adverse Event: An Adverse Event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporarily associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. All AEs must be reported to the IRB on a reportable event log at continuing review or when reporting a Serious Adverse Event (SAE) or Unanticipated Problem (UP).

AEs should include any new events not present during the pre-intervention period or events that were present during the pre-intervention period which increased in severity.

Severity: The severity of adverse events is typically classified as follows:

- **Mild:** awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

- **Moderate:** events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe:** events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Note: severe is **not synonymous** with serious. A **severe** rash is not likely to be an **SAE**. Likewise, a **severe** headache is not necessarily an **SAE**. However, **mild** chest pain may result in a day's hospitalization and thus is an **SAE**.

Expectedness: The expectedness of adverse events should be classified as follows:

- **Unexpected:** nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- **Expected:** event is known to be associated with the intervention or condition under study.

Relatedness: The relatedness of adverse events to the study should be classified as follows:

- **Definitely Related:** The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- **Possibly Related:** An adverse event that follows a reasonable temporal sequence from administration of the study intervention or follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- **Not Related:** The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Serious Adverse Event: A Serious Adverse Event (SAE) is defined as any adverse event temporarily associated with a subject's participation in research, **regardless of relatedness**, that meets any of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - Note: hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Therefore, participants do not need to be hospitalized overnight to meet the hospitalization criteria. Hospitalization (including hospitalization for an elective procedure) for a preexisting condition (prior to study entry) which has not worsened does not constitute a serious event.
- Results in a persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect
- Any other adverse event that, 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)

Unanticipated Problem: Unanticipated Problems Involving Risk to Subject or Others (UPIRSO, or just UP for short) can be either **AE/SAEs**, which are unexpected events that relate directly to participant safety, or **protocol deviations** that put patient privacy at risk or put patients at risk in some way that does not have an impact on their health and safety. Any incident, experience, or outcome that meets **all** the following criteria would be classified as a UP:

- **Unexpected (in terms of nature, severity, or frequency)** given: (a) the research procedures described in the IRB-approved protocol and informed consent document, and (b) the characteristics of the participant population being studied,
- **Related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), and
- **Suggests that the research places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

SAEs that are unexpected and related or possibly related to participation in research are considered to be UPs because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Using the criteria above, investigators must consider each problem, event, or new information and decide whether it represents an AE or SAE and/or if it meets the criteria for a UP. The IRB needs information about these events and/or problems to determine that (a) risks to participants are minimized, and (b) the risks are reasonable in relation to the anticipated benefits.

Responsible Parties

The Institutional Review Board (IRB) is responsible for:

- Reviewing reportable events in a timely fashion,
- Being a steward of a research environment that promotes the responsible conduct of research, and
- Determining whether the reported event meets the threshold of an unanticipated problem involving risk to subjects or others

The Office of Scholarly Activity (OSA) is responsible for:

- Fostering a research environment that promotes the responsible conduct of research,
- Providing the necessary support to investigators and the IRB,
- Supporting investigators in helping submit reportable events,
- Developing written policies and procedures for addressing reportable events,
- Monitoring compliance with this SOP, and
- Posting this SOP for the PNWU community.

The Investigator is responsible for:

- Documenting and reporting unanticipated problems in a timely manner,
- Assessing unanticipated problems,
- Communicating with the IRB Chair, IRB Administrator, and OSA staff in a timely fashion, and
- Seeking support from OSA and the IRB on proper reportable event submission and any necessary protocol revision.

Definitions

Please reference the Glossary for complete definitions of the following terms and additional terms not listed.

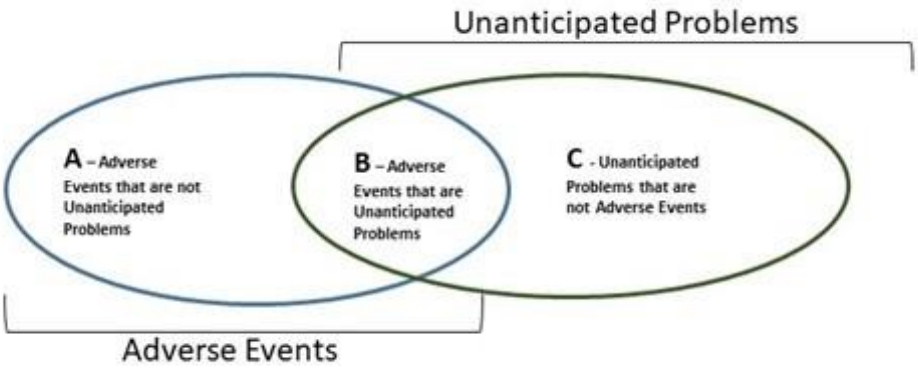
- Adverse Device Effect
- Adverse Events
- Adverse Finding/Reactions
- Clinical Trials of Investigational Medicinal Products (CTIMPs)
- Corrective And Preventive Action (CAPA) Plan
- Federal wide Assurance
- Institutional Review Board (IRB)
- Institutional Official (IO)
- Reportable Event
- Serious Adverse Events
- Suspected Serious Adverse Reactions
- Suspected Unexpected Serious Adverse Reactions
- Unanticipated Problems

Procedure:

Initial Assessment and Reporting

1. The principal investigator (PI) is responsible for reviewing incidents, problems, events, experiences, or outcomes and determining whether they represent an AE or SAE and/or if they meet the criteria for a UP.
2. Investigators and their study staff are responsible for reporting UPs via the electronic IRB system **within 14 days of discovery**.
3. SAEs must be reported **within 7 days of discovery**.
    - If the SAE involves the death of a participant, the investigator must contact the IRB Chair, IRB Administrator, or IO **immediately upon discovery**. Investigators must submit a follow-up report in the electronic IRB system **within 7 days**.
4. AEs that do not meet the definition of a UP do not need to be reported immediately to the IRB. Instead, these should be recorded on the study's reportable event log which is then provided to the IRB **at the time of continuing review OR annual check-in**. Investigators must track AEs in order to determine that they are not occurring more frequently than expected and that the events are not more severe than expected.
5. Event reports should include the following:
    - A corrective and preventative action plan (CAPA) when applicable. The CAPA plan must address what will be done to correct the problem and prevent future occurrences.
    - A copy of the study's reportable event log.
6. Anyone who is not a member of the research team may report concerns of possible UPs to the IRB Chair, IRB Administrator, IO, or via the PNWU confidential reporting form on the Office of Compliance, Ethics, and Integrity Services webpage.

7. If an individual, whether investigator, study staff, study participant, or other, is uncertain there is an SAE or UP to report, he or she may contact the IRB Chair or IRB Administrator to discuss the situation informally and receive guidance as to whether or not the event is reportable.



Adapted from the image in the HHS Guidance for Unanticipated Problems and Adverse Events. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

IRB Management of Event Reports

1. Upon receipt of an event report, the IRB Administrator pre-reviews the submission within 10 business days. If needed, the IRB Administrator contacts the investigator for corrections, clarifications, or additional information.
2. If someone other than the investigator filed the report, a written report summarizing the available information will be developed by the IRB Chair or their designee (e.g., the IO, IRB Administrator, member of the IRB, or assigned staff). The IRB Administrator will upload the written summary into the electronic IRB system.
3. The IRB Chair or designated reviewer receives and reviews the event report to determine whether it meets the definition of a UP. If needed, the reviewer may request additional information from the investigator or others.
4. If the reviewer determines that the event did not meet the definition of a UP, the IRB Administrator will notify the PI that no further action is needed.
5. If the event meets the definition of a UP, the IRB may take any the following actions:

    a. Accept report with no additional requirements,
    b. Approve investigator's proposed change,
    c. Place an administrative hold on the study pending IRB receipt of further information from the PI in a time period not to exceed 90 days,
    d. Conclude that the event meets the definition of noncompliance (e.g., protocol deviation, misconduct) and request additional information from the study team or require further actions such as, but not limited to, requiring additional training of members of the study team,
    e. Require a full board review at a convened meeting,
    f. Require modification of the protocol,
    g. Require modification of the consent form or information disclosed during the consent process,
    h. Require the study team to provide additional information to current participants (e.g., when the information may relate to the participant's willingness to continue participation),

i. Require that arrangements are made for clinical care outside the research or additional follow-up for participants,
j. Require the study team to provide additional information to past participants,
k. Require re-consent of current study participants,
l. Alter the frequency of continuing review,
m. Observe the research or the consent process,
n. Notify investigators at other sites, and/or
o. Terminate or suspend the research. If this action is taken, the IRB Chair will notify the IO to initiate any reporting actions.

6. Reportable events that are not reviewed by the full board will be summarized and reported to the members of the IRB at the next scheduled meeting.
7. If at any point it is believed that the information suggests that subjects may be at risk of harm without immediate intervention, the IRB Chair and the IO must be notified so that necessary steps can be taken to ensure the safety of subjects or investigate the event. The IO and IRB Chair have the authority to suspend the study should the need arise.
8. If the study is federally funded (e.g., HRSA, NIH, DoD), the IRB will report the UP to the IO who will then report the UP to the funding agency if required.

References:

1. Code of Federal Regulations, Title 45, Public Welfare, Department of Health and Human Services Part 46, Protection of Human Subjects, Revised January 15, 2009, Effective July 14, 2009
2. Department of Health and Human Services, Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection, May 5, 2004.
3. Code of Federal Regulations, Title 42 Policies of General Applicability, Department of Health and Human Services, Part 50 Subpart F – Promoting Objectivity in Research
4. OSA SOP 104: Scope and Authority of the IRB
5. OSA SOP 124: Review and Approval of Studies
6. OSA SOP 129 Required Reporting: Protocol Violations, Deviations and Noncompliance

Version/ Effective Date	Author	Section Changed & Reason for Revision
.00 / 06-30-2020	C. Case	Original SOP - Per HRP recommendations to separate Unanticipated problems and Noncompliance into two SOP.
.01 / 1-25-2023	C. Case	Note at the bottom of page 3 that covers unexpected problems and reporting at the time of continuing review revised to include reporting at the time of annual check-in for those studies not required to undergo annual continuing review.
.02 / 4-2-2024	J. Simmons	Fixed broken link to PNWU confidential reporting form. Now processed by the Office of Compliance, Ethics, and Integrity Services.

.03 / 8-26-2024	J. Simmons	Significant updates throughout to improve clarity of terms, criteria, and procedures. Added requirement that SAEs involving the death of a participant be reported immediately and directly to the IRB Chair, Administrator or IO with a follow-up report due 7 days later (as with other SAEs).

Appendices: