Procedure Title: Required Reporting: Protocol Deviations/Violations/Noncompliance

Associated Policy:	Human Research Protection Policy (OSA Policy 1.0)		
Responsible Unit:	Office of Scholarly Activity		
Created:	2/5/2020	**Executive Lead:**	Chief Research Officer
Effective:	3/24/2020	**Revision History:**	.00 – 2-6-2020; .01 – 09-28-2020; .02 – 03-18-2021; .03 – 8-01-2022; .04 – 2-14-2023; .05 – 6/01/2023; .06 – 4/2/2024
Approved by:	Institutional Review Board		
Procedure Number:	129.06		
Key Words:	Reportable Event, Protocol Deviation, Protocol Violation, Corrective and Preventative Action Plan (CAPA), Noncompliance		
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 noncompliance 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 events. SOPs are not intended to supersede existing institutional policies, and local, state, and federal laws and regulations.

General Information:
The ethical conduct of research is a shared responsibility requiring collaboration, cooperation, and trust between all members of the research community and the subjects who enroll in research.

Noncompliance is action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations, state laws, the approved study protocol and procedures, IRB directives, IRB requests, or determinations of the IRB. Noncompliance can be unintentional or intentional and may vary in nature, severity, and frequency. The review and resolution of noncompliance depends on the seriousness or repetitive nature of the noncompliance.
Serious noncompliance is a failure to adhere to the laws, regulations, or policies governing human research that may reasonably be regarded as: (1) Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or (2) Substantively compromising the effectiveness of a facility's human research protection or human research oversight programs. *(Source: SAEs, UAP, and Deviations: The What, When, Where, and How of Reporting Events to the VA Central IRB)*

- The IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance. Multiple instances of minor noncompliance are continuing noncompliance; however, they may constitute serious noncompliance when considered collectively. The Board may consider mitigating factors, such as corrective action taken, that play a role in the determination of whether the event increased risk, decreased potential benefits, or negatively affected the integrity of the human research protection program, but if despite these factors, the event meets the definition of serious noncompliance, then the event should be categorized as such. The determination of serious noncompliance is at the discretion of the IRB.

Minor noncompliance typically involves administrative oversights, non-substantive changes, or any other noncompliance that does not adversely affect the rights, safety, or welfare of research subjects.

Continuing noncompliance is a pattern of noncompliance that if allowed to continue, in the judgment of the IRB chair or convened IRB, may result in serious noncompliance. Continuing noncompliance also includes failure to respond to a request to resolve an episode of noncompliance.

Responsible Parties

The Institutional Review Board (IRB) is responsible for:

- Being a steward of a research environment that promotes the responsible conduct of research
- Reviewing reportable events of noncompliance in a timely fashion
- Determining whether the event meets the threshold of serious noncompliance or continuing noncompliance
- Assessing and investigating, as directed by the IRB Chair or Institutional Official, allegations of noncompliance.

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

- Providing a secure, confidential environment to protect people coming forward with allegations of research misconduct.
- Having an institutional assurance of compliance with this SOP
- Developing written policies and procedures for addressing allegations of research noncompliance, with subsequent approval by the IRB.
- Responding to each allegation and enacting the evaluation in a thorough, competent, objective, and fair manner.
- Fostering a research environment that promotes the responsible conduct of research
- Posting this SOP for the PNWU community
- Protecting the public health, federal funds, and equipment, as well as the integrity of funded research

The Institutional Official is responsible for:

- Responding to each allegation in a thorough, competent, objective, and fair manner.
- Assessing whether the allegation/complaint:
  - falls within the definition of misconduct in research, scholarship, or creative works
  - is sufficiently credible and specific to warrant an inquiry
  - pertains to funding (e.g., federal, state, local, and/or private)
- Directing the IRB in an investigation

The Research Integrity Officer is responsible for:

- Assessing allegations of research misconduct to determine if they fall within the definition of research misconduct, as set forth in the PNWU Research Misconduct Policy and Procedures, 42 CFR Part 93 or other applicable law, and warrant an inquiry on the basis that the allegation is sufficiently credible and specific so that potential evidence of research misconduct may be identified; and overseeing inquires and investigations as set forth in the PNWU Research Misconduct Policy and Procedures

The Investigator is responsible for:

- Being a steward of a research environment that promotes the responsible conduct of research
- Seeking support from OSA and the IRB on proper reporting for noncompliance and necessary protocol revision
- Maintaining well-organized, accurate, and robust research files for all studies should steps need to be taken to obtain custody of relevant research records
- Ensuring compliance with the IRB-approved protocol, federal regulations, state laws, good clinical practice, and FDA guidance
- Documenting and declaring any reportable events related to human subjects' research
- Cooperating with the investigations of allegations of research noncompliance

Definitions

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

- Audit
- Continuing Noncompliance
- Corrective And Preventive Action (CAPA) Plan
- Federal Wide Assurance
- Institutional Review Board
- Institutional Official (IO)
- Noncompliance
- Protocol Deviation/Protocol Noncompliance
- Reportable Event
- Unanticipated Problem

Noncompliance Reporting Procedures:

1. The principal investigator (PI) is responsible for reviewing any possible instance of noncompliance or deviation from a research protocol that has not been approved in advance by the IRB.
2. Investigators and their study staff are required to report instances of protocol deviation and possible noncompliance to the IRB within 10 working days of discovery.
3. If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the Institutional Official the IRB Chair, or the IRB Administrator, to discuss the situation informally.
4. Investigators and their study staff must complete and submit the Event Report Form in the IRB electronic system. The event report requires a corrective and preventative action plan (CAPA). The CAPA plan must address what you will do to correct the problem and prevent future occurrences. The reporting form also requires the study team to attach a copy of the study event reporting log.
5. Additionally, anyone may report concerns of possible noncompliance to the IRB Chair, Institutional Official, or the IRB Administrator verbally or in writing or via the PNWU confidential reporting form on

the Office of Compliance, Ethics, and Integrity Services' webpage. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

6. Information regarding noncompliance in human participant studies may come to the attention of the IRB through other pathways, including information contained in new applications, continuing reviews, adverse experience reports, reports from collaborators, employees, participants, or others

Noncompliance Review Procedures:

1. The IRB reviews and oversees allegations of noncompliance. Any additional allegations of Research Misconduct are investigated separately as outlined by the PNWU Policy on Research Misconduct and SOP 153.
    - Research Misconduct is fabrication, falsification, plagiarism in proposing, performing, or reviewing research, or in reporting research results.
    - In cases that involve allegations of research misconduct, the IRB Chair contacts the Research Integrity Officer (RIO) for further action.
    - The RIO will keep the IRB and IRB Chair informed of progress of any Research Misconduct proceedings and coordinate with the IRB and IRB Chair as appropriate,

2. Upon receipt of the event report of possible noncompliance, the IRB Administrator pre-reviews the submission. If needed, the IRB Administrator contacts the investigator for corrections, clarifications, or additional information. The IRB Administrator will complete pre-reviews within 7 business days. Review will occur regardless of when the event occurred.

3. If someone other than the investigator or member of the study team filed the report, a written report summarizing the available information will be developed by the Institutional Official (IO), IRB Chair, IRB Administrator or assigned staff. The written summary will be completed within 7 business days and provided to the IRB Administrator to upload into the IRB electronic system and notify the investigator. If the information suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the IRB Chair, and, when appropriate, the IO will be notified so that any necessary steps can be taken to ensure the safety of subjects or investigate the matter. The IO and IRB Chair have the authority to suspend or terminate the study should the need arise.

4. The IRB Chair, Vice Chair, or designated reviewer receives and reviews the event report and makes an initial determination as to whether the event represents noncompliance, and, if so, if the noncompliance may be serious or continuing. If needed, the reviewer may schedule an inquiry meeting or request additional information from the investigator or others. When inquiry meetings are held, the investigator will receive a written summary report within 10 business days. When circumstances warrant, the IRB Chair or IRB Administrator may bypass this step and assign the report for convened board review.

5. If the reviewer determines that the event or issue does not meet the threshold of noncompliance, or the event is noncompliance but not serious or continuing noncompliance, they will review any proposed corrective and preventative action plans (CAPA) and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are required. As warranted, the reviewer may refer the matter to the convened IRB for review. Review results will be recorded in the electronic IRB system and communicated to the investigator in writing.

6. If the reviewer determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is serious or continuing noncompliance. The IRB will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are necessary to ensure the protection of human subjects.
    a. The Board may consider mitigating factors, such as corrective action taken, that play a role in the determination of whether the event increased risk, decreased potential benefits, or negatively affected the integrity of the human research protection program, but if despite these factors, the event meets the definition of serious noncompliance, then the event should be categorized as such.
    b. Multiple instances of noncompliance that are deemed not serious individually, may constitute serious noncompliance when considered collectively.
    c. The IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance. The determination of serious noncompliance is at the discretion of the IRB.
    d. Results of the IRB Meeting will be recorded in the IRB minutes and communicated to the investigator in writing.

7. The IRB may take additional actions or require additional actions from the investigator or study team to ensure the protection of human subjects. These actions include, but are not limited to:

    a. Requiring modifications to the protocol or research plan
    b. Revising the continuing review plan or reporting timeline
    c. Modifying the consent process
    d. Modifying the consent document. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
    f. Providing additional information to past participants
    g. Requiring additional training of the investigator and/or study staff
    h. Requiring that current subjects re-consent to participation
    i. Monitoring the research
    j. Monitoring consent
    k. Reporting or referral to appropriate parties (e.g., the IO, Compliance, Risk Management, Privacy)
    l. Suspending IRB approval
    m. Terminating IRB approval
    n. Require further assessment of the noncompliance
    o. Other actions as appropriate given the specific circumstances

Reporting Procedures:

1. When the IRB determines that an event is serious or continuing noncompliance, or the event is unanticipated in nature, severity or frequency, the IRB staff will notify the IO. The IO or a designee (IRB Chair, IRB Administrator) will follow the procedures for reporting to regulatory agencies (e.g., OHRP, FDA), sponsors, and organizational officials. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

2. When further investigation is necessary, the IO, or designee, initiates the assessment process. The assessment process for a serious noncompliance or continuing noncompliance must be completed within 60 calendar days of its initiation by

a. Notifying appropriate institutional officials, The Institutional Review Board Chair, the principal investigator, and if necessary, federal agencies, that an inquiry has been initiated.
b. Sequestering records related to the assessment by IO or designee
c. Notifying the PI and seeking information (interviews and collection of resources/data) from the PI, other investigators, research subjects and any other relevant sources or records.
d. Determining whether outside expertise is needed.
e. Developing an assessment report

3. Investigators may request that the IRB reconsider its determination by following the procedures in SOP 108 Appeal of IRB Decisions.

References:

1. Food and Drug Administration (FDA) Federal Regulations (21 CFR 50, 54, 56, 312, 314, 600, 601, 812 and 814) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
2. Department of Health and Human Services (DHHS) Regulations (45 CFR 46 Subparts A, B, C, and D) http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
3. Title 21 CFR part 11 - Electronic Records; Electronic Signatures
4. Title 21 CFR parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards)
5. Title 21 CFR part 312 (Investigational New Drug Application), part 312.62 Investigator Record Keeping and Record Retention for Clinical Drug or Biological Trials
6. Title 21 CFR part 812 (Investigational Device Exemptions), part 812.140 Investigator Record Keeping and Record Retention for Device Trials
7. Title 42 CFR 50 - Public Health Service Policies on Research Misconduct
8. Title 42 CFR 93 - Public Health Service Policies on Research Misconduct
9. ICH GCP Consolidated Guidance Part 4.9 Records and Reports
10. ICH GCP Consolidated Guidance Part 5.15 Record Access
11. FDA Compliance Program Guidance Manuals 7348.811 – Investigators and 7348.810 – Sponsors/CROs/Monitors
12. FDA Investigations Operations Manual. PNWU Research Misconduct Policy
13. 45 CFR Part 93 HHS Public Health Policies on Research Misconduct

Revision History:

Version/ Effective Date	Author	Section Changed & Reason for Revision
.00 / 3-24-2020	C. Case	Original SOP
.01 / 09-28-2020	C. Case	Additional information added to item 5 (a, b & c) regarding determinations of the IRB, mitigating factors, corrective actions, and serious noncompliance.
.02 / 03-11-2021	C. Case	Replaced serious noncompliance paragraph and continuing noncompliance paragraph in the General Information Section; Revised continuing noncompliance definition; revised noncompliance review procedures item #2 to include termination.
.03 / 09-08-2022	B. Roach	Minor modification to the definition of noncompliance; added definition of serious noncompliance; added directing the IRB

		in investigations to the institutional officials role; added roles for research integrity officer; added item 6 under noncompliance reporting procedure regarding how information about noncompliance may come to the IRB; added item 1 under noncompliance review procedures regarding the IRB review and oversight of response allegations of noncompliance and other allegations of research misconduct governed by the PNWU Policy on Research Misconduct; added reference to the PNWU Research Misconduct Policy in the reference section.
.04 / 2.14.2023	C Case	Renumbered references at the bottom of the SOP (they were misnumbered). Added reference for 42 CFR Part 93 HHS Public Health Policies on Research Misconduct
.05 / 6.1.2023	C. Case	Adding a section for reporting procedures and renumbering the items that are related to reporting. Added the ability to designate a designee to file reports with regulatory agencies.
.06 / 4.2.2024	J. Simmons	Fixed broken link to PNWU confidential reporting form. Now processed by the Office of Compliance, Ethics, and Integrity Services.

Appendices:
None