Sponsor-Issued Safety Reports	CR-215
Clinical Research Standard Practices	**Effective Date:** December 2024

SCOPE AND PURPOSE This document is applicable to the following roles within Penn State College of Medicine and Penn State Health entities engaged in clinical research:

X	Principal Investigator	X	Regulatory Specialists
X	Sub-Investigators		Key Study Ancillary Personnel
X	Study Coordinators/Associates	X	Financial Analyst/Contract Management Accountants
	Data Specialist	X	Central Research Office Personnel

This policy describes how sponsor-issued safety reports will be managed. The policy applies to all studies where Penn State College of Medicine and Penn State Health (collectively, "Investigative Site") is:

- Only a participating site in a multicenter trial, and
- Not the coordinating center, study sponsor, responsible party, and
- Not the regulatory sponsor, IND holder, or IDE holder.

FDA guidance defines an Unanticipated Problem as an event that is:

- Unexpected (in terms of nature, severity, or frequency) given the risks described in the protocol-related documents (e.g., Investigator's Brochure, study protocol, informed consent form) and the characteristics of the participant population being studied;
- Related or possibly related to the investigational article (possibly related means there is a reasonable possibility that the experience or outcome may have been caused by the investigational article); and
- Suggests that the clinical trial places participants or others at a greater risk of harm than was previously known or recognized.

Furthermore, an Unanticipated Problem can be:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an Unanticipated Problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human participants (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control).
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents

a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison

- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human participants.

External Safety Reports are adverse event (AE) reports that are distributed from external sponsors, regarding an event that is experienced by non-Investigative Site participants of a clinical trial. These may be referred to as Suspected Unexpected Serious Adverse Reaction (SUSARs),
Investigational New Drug (IND) Safety Reports (INDSRs), alerts from sources such as Council for International Organizations of Medical Sciences (CIOMS) or Medwatch, and safety or adverse alerts from sponsors or CROs via online portals or distribution lists.

Office for Human Research Protections (OHRP) under the U.S. Department of Health and Human Services (HHS) notes that reports of individual external AEs often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the AEs are unexpected, related or possibly related to participation in the research, or suggest that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized.

OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR 46 for reports of individual AEs occurring in participants enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual AEs should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an Unanticipated Problem.

In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external AEs. Ideally, AEs occurring in participants enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

In accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP), it is the responsibility of Sponsor to notify investigators, IRBs, and regulatory authorities of all adverse drug reactions that are both serious and unexpected. By nature, drug reactions would indicate a causal relationship between the event and the drug. A causal relationship would indicate that the event is related, probably related, or possibly related to the drug.

Federal regulations require the sponsor of an Investigational New Drug (IND) or Investigation Device Exemption (IDE) study to promptly review all information relevant to the safety of the drug and to consider the significance of the report within the context of other reports (21 CFR 312.32). Furthermore, the regulations state that for studies conducted under an IND or IDE, investigators must report all Unanticipated Problems to the IRB.

Food and Drug Administration (FDA) recognizes that for multicenter studies, the sponsor is better positioned to process and analyze AE information for the entire study and to determine

whether an AE occurrence is both unanticipated and a problem for the study. The sponsor is able use information from multiple study sites or other information not readily accessible to the individual investigators (e.g., a sponsor's preclinical data, etc.) to make the necessary determination. Therefore, FDA guidance is for the sponsor to determine if an AE is an Unanticipated Problem, and once determined to be an Unanticipated Problem, the AE is reported to the IRB by the investigator or designee. In instances where a central IRB is utilized, the sponsor would be reporting directly to the central IRB as the IRB of Record.

It is the policy of Investigative Site that external safety reports are not required to be reviewed by the Principal Investigator (PI) or Sub-Investigator (Sub-I), unless contractually obligated.

This policy is intended to be shared externally.

POLICY AND PROCEDURE STATEMENTS

1. Safety Reports Received by Email
    a. Safety reports received by email should be sent to a study team group email or distribution list when possible.
        i. Sponsors must not send safety reports to the PI without including a study team member or study team group email or distribution list.
        ii. Sponsors are prohibited from sending safety reports directly to the Clinical Trials Office, Investigational Drug Service, IRB, Office of Research Affairs, or other central research offices.
    b. Safety reports received by email should be stored in accordance with *CR-211: Regulatory Files and Participant Records.*
    c. Safety reports that Sponsor has explicitly designated as being a reportable Unanticipated Problem are to be reviewed by the local PI as noted below and reported promptly to the IRB of Record in accordance with the IRB's policies and procedures.

2. Safety Reports Received through a Portal
    a. The PI or delegate shall acknowledge all safety reports in Sponsor's portal. By acknowledging the safety report in the portal, the individual is confirming receipt of the report and processed in accordance with this policy.
        i. It is the policy of Investigative Site that a PI should not expected to personally acknowledge all safety reports in Sponsor's portal.
            - If a PI is expected to personally acknowledge all safety reports in Sponsor's portal due to contractual obligations or protocol requirements, proper remuneration will be provided by the Sponsor.
        ii. Sponsor will provide proper remuneration if safety reports need to be opened individually to be acknowledged.
        iii. Sponsors are prohibited from sending safety reports directly to the Clinical Trials Office, Investigational Drug Service, IRB, Office of Research Affairs, or other central research offices.
    b. Safety reports received through a portal do not need to be downloaded.
        i. If required by contract or protocol, the safety reports will be downloaded and stored in accordance with *CR-211: Regulatory Files*

and Participant Records with proper remuneration provided by the Sponsor.

c. Safety reports that Sponsor has explicitly designated as being a reportable Unanticipated Problem are to be reviewed by the local PI as noted below and reported promptly to the IRB of Record in accordance with the IRB's policies and procedures.

3. Review of Safety Report Document
   a. The PI or study team will only review external safety reports in which the sponsor has explicitly specified that the event has been determined to be an Unanticipated Problem.
   b. The following information should be included in the safety report:
      i. A clear explanation of why the adverse event(s) have been determined to be unexpected.
      ii. The implication for the conduct of the trial (e.g., change to the protocol, informed consent investigator brochure, etc.)
   c. When a safety report has met the criteria outlined above for an Unanticipated Problem, the report will be reviewed by the PI or physician sub-investigator. If the PI agrees with the sponsor's assessment, the report and associated documents (i.e., protocol amendment, etc.) will be submitted to the IRB of Record in accordance with that IRB's policy.

RELATED POLICIES AND REFERENCES

Clinical Research Guidebook (https://research.med.psu.edu/research-support/guidebook/)

Code of Federal Regulations: Investigational New Drug Application (21 CFR 312.32,33,44,812)

Code of Federal Regulations: Institutional Review Board (21 CFR 56.108, 109, 115)

Code of Federal Regulations: General requirements for Informed Consent (45 CFR 46.103, 109, 115, 116)

International Conference on Harmonization Good Clinical Practice E6(R2)

Food and Drug Administration: Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection (January 2009)

Office for Human Research Protections Guidance: Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html)

Responsibilities of the Research Team (CR-103)

Site-Sponsor/CRP Communications (CR-210)

Regulatory Files and Participant Records (CR-211)

Adverse Event Reporting (CR-304)

APPROVALS

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DATE OF ORIGIN AND REVIES
Date of origin: November 2023

Review Date(s):

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DEPARTMENT-SPECIFIC PROCESSES ADDENDA

The following departments and study teams have specific processes that are outlined below. These department-specific processes are to further define internal processes and not represent superseding policies or procedures.

Penn State Cancer Institute

Policy and Procedure Statements

1. Document Review
    a. The Penn State Cancer Institute Clinical Trials Office (PSCI-CTO) requires the sponsor to send qualifying reports directly to the PSCI-CTO primary site contact and study PI. PSCI-CTO will not review portals for safety reports. **Posting reports in a sponsor portal does not qualify as a means of direct reporting of an Unanticipated Problem.**
    b. The PSCI-CTO will only review external safety reports in which the sponsor has explicitly specified that the event has been determined to be an Unanticipated Problem as outlined in *CR-304: Sponsor-Issued Safety Reports*:
    c. Any report that has not met the criteria as an Unanticipated Problem will not be reviewed or retained by PSCI-CTO investigators or staff.
    d. If the trial is not covered by this policy, then the study PI may have the responsibility to review external safety reports.
    e. The PSCI-CTO considers that the study sponsor, in conjunction with the study's DSMB/DSMC, is accountable for:
        i. Receiving and reviewing reports of safety events (e.g., SAEs, etc.) from all participating sites;
        ii. Evaluating the overall importance of the events from all sites;
        iii. Determining if an event is considered an Unanticipated Problem, per OHRP guidance; and
        iv. Determining if an event(s) warrants additional action such as revision or suspension of the study.

2. Reporting Requirements
    a. The PSCI-CTO, in accordance with OHRP guidance from January 2007, states that any event, which, in the opinion of the investigator, is determined to be an Unanticipated Problem, should be reported to the IRB.
    b. An event must meet all criteria to be considered an Unanticipated Problem which meets reporting requirements to the Penn State Health IRB:
        i. unexpected or unanticipated; **and**
        ii. related or possibly related to the investigational drug/device; **and**
        iii. serious or otherwise one that suggests the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized and as such warrants changes in the research protocol or consent process.

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HISTORY OF REVIEWS AND REVISIONS

Month 202X	
Scope and Purpose	Updated "Financial Analyst/**Contract Management Accountants**". Added "Regulatory Specialists" and "Central Research Office Personnel."
Policy and Procedure Statements, Bullet 2.a.i.	Add statement that a history of reviews and will be maintained as an appendix to each Standard Practices.