THE OHIO STATE UNIVERSITY

EVENT REPORTING- UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS, ADVERSE EVENTS, AND OTHER PROBLEMS

1. Overview

Federal regulations require the university to have written procedures for ensuring that unanticipated problems involving risks to subjects or others are reported to the IRBs, appropriate institutional officials, and federal agencies. The IRB has the authority to suspend or terminate approval of research that is not conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

Unanticipated problems can occur in any type of research (medical or non-medical) and may include occurrences such as adverse events, subject complaints, protocol deviations, and other untoward events involving risk. Events requiring reporting by investigators and research staff may involve physical, psychological, social, legal, or economic harms.

2. Definitions

Unanticipated problems involving risks to subjects or others (UPIRSO): An incident, experience, or other problem that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, 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, even if no harm actually occurred.

Unanticipated problems involving risks to subjects or others may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse drug events and unanticipated adverse device effects (see below). OHRP guidance and examples of events that constitute a UPIRSO can be found here.

Adverse event (AE): Any undesirable and unintended (although not necessarily unexpected) effect occurring as a result of interventions, interactions, or collection of identifiable private information in research. In medical research, any untoward physical or psychological occurrence in research, including abnormal laboratory finding, symptom, or disease temporally associated with the use of (although not necessarily related to) a medical treatment or procedure. Adverse events involving drugs are also referred to as *adverse drug experiences*.

Serious adverse event (SAE): An adverse event that is fatal or life threatening, permanently disabling, requires or prolongs hospitalization, or results in significant disability, congenital anomaly, or birth defect.

Unexpected adverse event: An adverse event that has not been previously observed or is not consistent in nature, severity, or frequency with existing risk information, such as in the investigator's brochure, research protocol, consent form, or other available information (e.g., IND application for an investigational drug).

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; any other unanticipated, serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Related: Associated or having a timely relationship with; a reasonable possibility exists that an outcome may have been caused or influenced by the event in question (e.g., administration of a study drug), although an alternative cause/influence may also be present. Related events may be *definitely*, *probably*, or *possibly* related.

Unrelated: Unassociated or without a timely relationship; evidence exists that an outcome is definitely related to a cause other than the event in question.

Ohio State IRB jurisdiction: Research reviewed and approved by the Cancer, Biomedical Sciences, or Social and Behavioral Sciences IRB.

Internal event: An event occurring in Ohio State research at a site(s) under an Ohio State IRB's jurisdiction.

External event: An event occurring at a non-Ohio State site over which another IRB has jurisdiction in research that is also occurring at Ohio State.

3. Events Requiring Reporting

A. Investigators and research staff are responsible for reporting to the IRB unanticipated problems involving risks to subjects or others. Such reports may include adverse events (regardless of severity), subject complaints, protocol deviations, and other untoward events involving risk. Reports may also include events that are not categorized as adverse events and are not directly related to an individual subject's participation in a study, but represent risk to others. Events that do not cause detectable harm or adverse effects to subjects or others may still represent unanticipated problems.

B. Events that occur in Ohio State research that may represent unanticipated problems involving risks to subjects or others should be reported. For the timeframe for such reporting, see section 4 below. The following events may represent unanticipated problems involving risks to subjects or others:

- Adverse device effects that are serious, unanticipated, ***and*** related
- Adverse events or injuries that are serious, unexpected, ***and*** related

- Breaches of confidentiality involving risks
- Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile
- Events requiring reporting according to the protocol, sponsor, or funding agency
- New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings)
- Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures possibly involving risks or with the potential to recur, even if no harm has actually occurred
- Subject complaints indicating an unanticipated risk, or complaints that cannot be resolved by the research staff
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject
- Audit findings, inquiry, or written report by a federal agency (e.g., FDA Form 483)
- Suspension by the sponsor, investigator, or institutional entity
- Other problem or finding (e.g., loss of study data or forms, a subject becomes a prisoner while participating in research, etc.) that an investigator or research staff member believes could influence the safe conduct of the research.

Note: Concerns of noncompliance should be reported to the IRB via an event report application in Buck-IRB, regardless of the incident's potential effect on risk level. For more information on noncompliance reporting, refer to HRPP policy [Noncompliance].

For event reporting examples, go here.

4. Timeframes for Reporting

A. The events described above should be reported to the IRB using the Event Report application in Buck-IRB **within 10 days** of the investigator's or research staff member's learning of the event.

B. Events resulting in temporary or permanent interruption of study activities by the investigator, sponsor, or DSMB to avoid potential harm to subjects should be reported **within 48 hours.**

C. Events that may represent unanticipated problems involving risks to subjects or others should be reported (as described in section 3.B.), regardless of whether they occur during or after the study, or involve a subject who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past participants, an amendment request must also be submitted for IRB review.

D. Additional sponsor reporting requirements and timeframes may exist that are not outlined in this policy.

5. Events Not Requiring Reporting

A. Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") should be described in the informed consent process/form and do not require reporting to the IRB by investigators and/or research staff. The following are examples of events that ***do not*** require reporting:

- Adverse device effects that are non-serious, anticipated, ***or*** unrelated
- Adverse events or injuries that are non-serious, expected, ***or*** unrelated
- Deaths not attributed to the research, e.g., from "natural causes," accidents, or underlying disease and the investigator has ruled out any connection between the study procedures and the participant's death
- DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile
- Investigator's brochure updates not involving safety information
- IND safety reports from external sites not involving Ohio State research
- Protocol deviations or violations unlikely to recur or not involving the possibility of risks to subjects
- Subject complaints that were resolved or complaints not involving risks
- Problems or findings not involving risk (unless the investigator or research staff member believes the information could affect participants' willingness to continue in the research).

B. Events that occur at external sites that **do not involve** research conducted at Ohio State are not required to be reported via an event report. If the investigator plans to change the research protocol or informed consent document as a result of an external event, an amendment should be submitted through Buck-IRB. Investigators should retain copies of all external reports and are responsible for assessing whether the report meets reporting requirements. Any change to the risk benefit ratio should be explained in summary at the time of continuing review; individual external reports should **not** be provided as part of the continuing review submission.

For event reporting examples, go here.

6. Review Process

Event reports and accompanying information will be screened for completeness by ORRP staff members, additional clarifications will be requested from the investigator as necessary. ORRP staff members will make an initial determination about whether the event represents a possible unanticipated problem involving risks to subjects or others and/or potential noncompliance. Reports of events determined during screening to represent possible unanticipated problems involving risks to subjects or others and/or serious/continuing noncompliance will be forwarded to the IRB for convened review. Reports of events that do not meet the requirements for reporting will not be forwarded for IRB review. All other event reports will be reviewed by expedited procedure.

A. Expedited Review

Event reports and accompanying information will be forwarded by ORRP staff members to the appropriate IRB Chairperson, Vice Chair, or one of the experienced members with relevant expertise designated by the Chair for expedited review. Reviewers will have access to the complete protocol file, including previously reported events, for review. The Chairperson or designee will determine if the report raises new concerns about risks and will recommend further review by the convened IRB, as necessary, for a final determination. The IRB Chair or Vice Chair may suspend or terminate approval of an investigator's research if necessary to assure the protection of research participants. The Chair or Vice Chair will consider the rights and welfare of participants when suspending, terminating, or modifying research.

If during expedited review the event is determined not to be an unanticipated problem involving risks to subjects or others, the reviewer will make any necessary recommendations for action (see below), which will be communicated to the principal investigator by ORRP staff. Further actions proposed by the investigator or IRB reviewer that represent minor changes will also be reviewed by the expedited procedure. IRB members will be informed of these expedited reviews as described in HRPP policy [Expedited and Administrative Review Procedures].

B. Convened Review

Reports of events determined during screening or expedited IRB review to represent possible unanticipated problems involving risks to subjects or others and/or serious/continuing noncompliance will be forwarded to the IRB for convened review. Further actions proposed by the investigator or IRB reviewer that represent more than minor changes will be reviewed by the convened IRB. The Chair, Vice Chair, or other member with relevant expertise will serve as the primary reviewer. Copies of the reports, all other information provided by the investigator, and current consent documents (or verbal scripts) with any proposed changes will be included in the review materials for each IRB member. Sections from the protocol, previous event reports, and other relevant information or reference materials will also be included, as applicable. The complete protocol file will be available to any IRB member upon request prior to or during the convened IRB meeting. *Note: Further actions proposed by the investigator or IRB reviewer that represent minor changes can be reviewed by expedited procedure.*

The IRB will determine by convened review whether the event is an unanticipated problem involving risks to subjects or others and if the event represents serious and/or continuing noncompliance. Action(s) will be based on the nature of the event, degree to which research participants are placed at risk, occurrence of previous problems, etc. The IRB will consider the rights and welfare of participants when suspending, terminating, or modifying research.

C. IRB Actions

The types of actions that the IRB may consider for any event include, but are not limited to:

- Modification(s) of the research protocol or procedures

- Modification(s) of the consent process or consent form
- Providing additional information to current research participants (required when such information may relate to their willingness to continue in the research)
- Providing additional information to past research participants
- Reconfirming consent of current research participants
- Requiring additional follow-up/monitoring for current and/or past research participants
- Monitoring of the research (including audits) or consent process
- Education or mentoring for the principal investigator and/or research staff
- Additional reporting, including modification of the continuing review schedule
- Requiring additional resources to support the investigator's research activities
- Placing limitations (e.g., restriction to co-investigator status) on the investigator's research activities or use of research data
- Suspending or terminating the research
- Referral to other appropriate university process (e.g., misconduct review).

The IRB's determination and action(s), including votes taken, will be recorded in the meeting minutes. The requirements for quorum and majority apply, in accordance with HRPP policy [IRB Composition and IRB Member Roles and Responsibilities]. Investigators will be notified in writing by ORRP staff of IRB decisions regarding events determined not to represent unanticipated problems involving risks to subjects or others and/or noncompliance following approval of the meeting minutes by the IRB Chair or Vice-Chair.

Suspended IRB approval may be reinstated, as appropriate, based on the outcome of the convened review. Investigators (and others) will be notified of IRB actions regarding events determined to be unanticipated problems involving risks to subjects or others as described below.

7. Institutional Reporting

If the IRB determines that an event represents an unanticipated problem involving risks to subjects or others, serious and/or continuing noncompliance, or if the Board suspends or terminates approval of research that is associated with unexpected serious harm to subjects, the appropriate internal and external persons and/or agencies will be notified in writing of the determination and reasons for the IRB's action(s) according to HRPP policy [IRB Reporting-Unanticipated Problems, Noncompliance, Suspensions, and Terminations] and in accordance with The Ohio State University's Federalwide Assurance. The content of the report will conform to OHRP requirements for incident reporting.

8. Record Retention

Records of reports and reviews of events representing possible unanticipated problems involving risks to subjects or others, including submission materials and communications, are retained by the Office of Responsible Research Practices for at least three years, in keeping with federal regulations, applicable state and local laws, and university policies.

9. Applicable Regulations/Guidance

21 CFR 50.25(b)(5), 21 CFR 56.108(b)(1), 21 CFR 812.150(a)(1), 45 CFR 46.103(b)(5)(i), 45 CFR 46.116(b)(5), OHRP "Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events Guidance" (01/15/2007), OHRP "Continuing Review Guidance" (11/10/2010), OHRP "Guidance on Reporting Incidents to OHRP" (06/20/2011)

10. History

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