Event Reporting- Unanticipated Problems Involving Risks to Subjects or Others, Adverse Events, Protocol Deviations, and Other Problems

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Background:

Federal regulations require the university to have written procedures for ensuring that unanticipated problems involving risks to subjects or others and certain protocol deviations are promptly reported to the IRBs, appropriate institutional officials, and federal agencies. Based on those reported events, the IRB has the authority to suspend or terminate approval of research if appropriate.

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 prompt reporting by investigators and research staff may involve physical, psychological, social, legal, or economic harms.

Q: What are the types of adverse events and when do they need to be reported to the IRB?

Unless otherwise indicated by the IRB, all adverse events must be reported to the IRB.

- **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.

- **Expected adverse event:** An adverse event that is known to occur from the research interventions. These should be listed in the consent form under potential research risks.

- **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).

Q: How should adverse events be reported to the IRB?

How adverse events are reported to the IRB is based on the seriousness and relationship of the adverse event to the research study interventions. Please see the above question for definitions.

- **Serious and Unexpected** adverse events must be reported to the IRB within 5 days of the PI becoming aware of the event. This requirement includes any death of a study subject. This
requirement also includes both local and non-local adverse events.

- **Serious or Unexpected local** adverse events only must be reported annually via the Cumulative Adverse Event Table which is uploaded with each Continuing Review.
  - Unexpected adverse events which are (a) related or possibly related, and (b) involve new risks to subjects or others meet the definition of an Unanticipated Problem and must be reported as described in the IRB Guideline titled “Unanticipated events-reporting”.

- **Not Serious and Expected local** adverse events only must be reported annually via the Cumulative Adverse Event Table which is uploaded with each Continuing Review.

**Q: How is the relationship of an adverse event to the research study determined?**

The relationship between an adverse event and the research study may be difficult to determine. One has to consider the type of event, the study interventions, and the time relationship between study interventions and the event. When reporting an adverse event, the IRB expects the Principal Investigator to provide their assessment of the relationship of the adverse event to the research study.

- **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.

**Q: Are there studies in which adverse events do not have to be reported to the IRB?**

Yes. All research studies that have been approved as minimal risk, only require the reporting of adverse events that the PI determines are Serious and Unexpected, and related. Also, upon request by the PI, the IRB may determine on a case-by-case basis, that the study is such that only Serious and Unexpected, and related adverse events need to be reported.

**Q: What if all study interventions are completed on all or some of my study subjects, what adverse events need to be reported to the IRB?**

When a study is originally approved as “greater-than-minimal” risk, and study interventions are completed on all or some of my study subjects, the only require reporting of adverse events are those that the PI determines are Serious and Unexpected, and related to the study in question.

**Q: What is an unanticipated problem that may involve risk to study subjects?**

OHRP considers unanticipated problems to include those events that:

- Are not expected given the nature of the research procedures that are described in the protocol-related documents and informed consent or consistent with the subject population being studied; and
• Suggest that the research places subjects or others at greater risk of harm or discomfort related to the research than was previously known or recognized.

• 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);

In order to determine if the unanticipated problem places subjects at greater risk of harm than was previously known or recognized is dependent on whether the event was related or possibly related to study participation in the research. The harm can be physical, psychological, economic, or social in nature.

For more information on reporting Unanticipated Problems, see IRB Guideline titled “Unanticipated events-reporting”.

Q: What are examples of Unanticipated Problems that present risk to subjects or others?

The following are examples of Unanticipated Problems that present risk to subjects or others:
• Any unapproved change or modification to an IRB approved protocol (deviation), intentional or unintentional, that places one or more subjects at risk or affects the integrity of study data;
• Changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a subject;
• Complaints that indicates unexpected risks, or complaint that cannot be resolved by the principal investigator;
• Malfunctioning of research equipment that results or could result in risk to subjects or others;
• Suspension of enrollment (by the investigator, sponsor) due to issues identified with the study that may involve risk to subjects;
• Events that requires prompt reporting to the sponsor (i.e. subject’s pregnancy)
• Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile
• Events requiring prompt 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)
• 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.

Q: How soon do unanticipated problems be reported to the IRB and how are they reported?

The events described above should be reported to the IRB using the Event Report application in myIRB within 5 working days of the event occurring or learning of the event via myIRB Reportable Event
submission form.

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.

Events that may represent unanticipated problems involving risks to subjects or others should be promptly 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.

Q: What is a protocol deviation?

A protocol deviation is any alteration/modification to study conduct within the IRB approved study on behalf of the PI or study staff without IRB approval. The term “study” encompasses all IRB-approved materials associated with the research including the protocol, protocol procedures, consent form, recruitment materials, questionnaires, and any other information relating to the research study.

Q: Are there different types of protocol deviations?

Yes. Deviations are broken in to two types: major and minor

- **Major Protocol Deviations** have the potential to negatively impact: the rights and welfare of the research subject, subject safety (increase risks and/or decrease benefits to study subjects) the subject’s willingness to continue to participate in the study, or integrity of research data.

  Submit these deviations to the IRB within 5 days of the occurrence or learning of the occurrence via Reportable Event in myIRB.

- **Minor Protocol Deviations** do not have the potential to negatively impact: the rights and welfare of the research subject, subject safety (increase risks and/or decrease benefits to study subjects) the subject’s willingness to continue to participate in the study, or integrity of research data.

  Submit these deviations to the IRB annually via the Minor Deviation Tracking Log that is uploaded with each Continuing Review.

Q: What are examples of Major Protocol Deviations?

Examples of Major Protocol Deviations include but are not limited to the following:

- Administering the incorrect dose of study medication.
- Failure to implement all protocol procedures resulting in increased risk or decreased benefit to the subject.
- Enrolling a study subject without proper informed consent.
- Enrolling a vulnerable subject population without receiving prior IRB approval.
- Enrolling ineligible subjects who have then gone on to receive study procedures.
- Implementing extra protocol procedures without IRB approval.
- Non-IRB approved research staff engaged in the research.
• Over enrollment of study subjects in a greater-than-minimal-risk study

Q: What are examples of Major Protocol Deviations?

Examples of Minor Deviations include but are not limited to the following:
• Study procedure conducted out of timeframe (e.g. blood drawn on day 10 when the protocol indicated every 7 days), and did not pose risk to subject
• Study visit out of timeframe, and did not pose risk to subject
• Participant failure to initial every page of the consent form
• Not all lab work ordered on a given visit, and did not pose risk to subject
• Copy of consent form not given to participant during informed consent process
• Participant failure to return diary
• Missing original signed consent, but have a copy of the participant signed consent

Q: What are examples of regulatory noncompliance?

Examples of regulatory compliance include, but are not limited to, the following:
Inadvertent oversight or delinquent timing in submitting a revision or SAE received from the study sponsor to the IRB within a specified timeframe
• Failure to report SAEs, unanticipated problems or deviations to the IRB/sponsor
• Use of the incorrect version of the ICF to enroll subjects
• Use of the incorrect protocol version/forms for research related activities
• Failure to obtain and/or document a subject’s Informed Consent (provided the IRB has not granted a waiver i.e. Informed Consent is required, but study procedures are initiated prior the consent form being signed, or an informed consent form is never signed).
• Failure to retain copies of signed Informed Consent forms (e.g. the PI lost one or more consent forms while moving offices, or cannot produce a signed consent form for all subjects enrolled in the study, etc.).
• Conducting research (including data collection) without active IRB approval (including after expiration of the protocol).
• Enrolling subjects without active IRB approval for the protocol (either prior to initial approval or during a period of expired approval). Includes research approved with a waiver of consent, such as survey or medical record research.
• Implementing a project revision without prior IRB approval (unless to protect the subjects against harm).
• Implementing planned protocol variations/exceptions without obtaining prior IRB approval – e.g. enrolling a subject who does not fit the inclusion/exclusion criteria specified in the protocol without prior IRB approval, continuing treatment on a subject who has met the definition of withdrawal per protocol.
• Recruiting/enrolling subjects at a location or in a manner that has not been previously approved.
• Conducting your research at a site or involving outside investigators without prior IRB approval.
Q: Does the reporting of Regulatory Noncompliance overlap with other reportable events?

Possibly. Regulatory Non-Compliance can lead to protocol deviations and/or adverse events, so it would not be uncommon to have (3) reportable events submitted at the same time. In myIRB you can select all applicable categories as needed.

Q: How are various Event Reporting reviewed by the IRB?

Event reports and accompanying information will be screened for completeness by UF IRB staff members, additional clarifications will be requested from the investigator as necessary.

An IRB Executive Reviewer will make an initial determination about whether the event represents a possible unanticipated problem involving risks to subjects or others and/or potential noncompliance. There are three potential outcomes; the Executive reviewer:

- Signs off on the event with no further action needed.
- Determines there is no immediate harm, but sends the event to the Full Board for further review.
- Considers the reported event serious enough to suspend the study, the IRB chair will be involved and make that final determination. If that is the determination, the IRB Chair will work with the PI to resolve any immediate study subject risk. In these cases the event is sent to the Full Board for further review.

Q: Are there any additional reporting requirements by UF?

Yes. 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, <insert P&P here> and in accordance with The University of Florida’s Federalwide Assurance. The content of the report will conform to OHRP requirements for incident reporting.