Event Reporting – Adverse Events, Unanticipated Problems Involving Risks to Subjects or Others, 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.

1. Q: What is an adverse event?

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 temporarily 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.

2. Q: What are the adverse events types?

- **Serious adverse event (SAE):** An adverse event that is fatal or life threatening, permanently disabling, requires inpatient hospitalization 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).

3. Q: How do you determine the relationship of an adverse event to the research study?

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 make a thorough assessment of the relationship of the adverse event to the research study.

- **Related:** Associated or having a timely relationship with the study intervention; or the event has a reasonable causal relationship to study interventions as judged by either the reporting investigator or the sponsor.
• **The relationship is “more likely than not”:** based on study interventions, the reporting investigator or the sponsor determines that a reasonable possibility exists that an outcome may have been caused or influenced by the study event in question (e.g., administration of a study drug); no plausible alternative cause/influence was present.

• **Unrelated:** Unassociated or without a timely relationship; evidence exists that an outcome is most likely related to a cause other than the event in question (e.g., disease progression).

4. **Q: Which adverse events must be reported to the IRB and when?**

When reporting an adverse event, the IRB expects the Principal Investigator to make a thorough assessment of the relationship of the adverse event to the research study.

• For all research studies, local and non-local: (5-day report)
  
  a. **Serious and Unexpected and Related or the Relationship is “more likely than not”** adverse events must be reported to the IRB within 5 days of the PI becoming aware of the event. Again, this requirement includes both local and non-local adverse events.

• For Greater-than-minimal Risk (GMR) Studies: (at Continuing Review only)
  
  a. Any other adverse event that is related to study interventions or the relationship to study interventions is “more likely than not”, that includes:
    i. Serious events that are expected, or
    ii. Unexpected events that are not serious, and
  b. All previously reported 5-day reports

5. **Q: Which adverse events “Do Not” need to be report to the IRB?**

• Any death or AE that is not consistent with these guidelines.
• Any non-local AE from a multi-center protocol that either has a DSMB or a study sponsor that is reviewing AEs

*If the IRB receives any death or AE required to be submitted by a study sponsor to the UF IRB that is not consistent with these guidelines, the UF IRB will simply acknowledge receipt.

6. **Q: Which study subject’s deaths need to be reported to the IRB?**

All study subject’s deaths, either local or not local, that the Principal Investigator has evaluated and considers the death to be either **related**, or the death is **“more likely than not”** related to study interventions must be reported to the IRB within 5 days of the Principal Investigator becoming aware or this death. These 5-day reports must be added to the Continuing Review report as described in item #4 above.

7. **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 or the relationship is more likely than
not to the study interventions in question.

8. **Q: What is an unanticipated problem and how is it reported to the IRB?**

   Please see Investigator Guideline on Unanticipated Problems.

9. **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.

10. **Q: Are there different types of protocol deviations?**

    Yes. Deviations are broken into 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.

11. **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.

12. **Q: What are examples of Minor Protocol Deviations?**

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

    - Study procedure conducted out of timeframe (eg. 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

13. Q: What events are considered Other Regulatory Noncompliance that must be reported to the IRB?

Other “Regulatory Noncompliance” includes errors and/or oversights involving the protocol, informed consent, and other regulatory paperwork associated with the study.

14. 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.

15. 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.

16. 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 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.

17. **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, [HRP-112](#) and in accordance with The University of Florida’s Federalwide Assurance. The content of the report will conform to OHRP requirements for incident reporting.