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Subject: Post-IRB Approval Reviews
Division: IRB
Date: March 1, 2012

IRB Policy 111.2: SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

Policy

If adverse consequences or unanticipated problems are encountered in the course of the study, or new information becomes available which could change the perception of a favorable risk/benefit ratio, the investigator is responsible for informing the IRB PROMPTLY. Based on this information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

Investigators must report Serious Adverse Events (SAEs) and unanticipated problems to the IRB within 48 hours of discovery, and 24 hours for deaths. For studies that have been determined by the IRB to be greater than minimal risk, these reports should be filed regardless of whether the SAE appears to be study related or is anticipated. For minimal risk studies, investigators must report only SAEs and unanticipated problems that they believe are possibly or definitely study-related. It is the IRB's responsibility (not the investigator's) to determine which studies are classified as minimal risk. Follow-up reports and a final written report should be sent to the IRB as soon as the investigator receives additional information regarding the event.

Definition of SAE

An SAE is one of the following events that may occur to a participant during a study:

1. Death, or a life-threatening event,
2. Hospitalization or prolongation of hospitalization,
3. Persistent or significant disability or incapacity,
4. Birth defect or congenital malformation,
5. Represents, in the PI's judgment, other significant hazards, or potentially serious harm to research participants or others, or
6. Any other event as defined in the research protocol.

Definition of Unanticipated Problem

Unanticipated problems, in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. 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;

2. Related or possibly related to participation in the research (in this policy, *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

3. 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.

Definition of Unexpected Adverse Event

An unexpected adverse event is any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Classification of Relatedness

The descriptions below should be used to grade the SAE's study-relatedness:

1. Not related: Clearly due to extraneous causes (e.g., underlying disease, environment)

2. Possibly: It is reasonable that the incident, experience, or outcome may have been caused by the procedures involved in the research

3. Definitely: Clearly related to the research

IRB Review

When a SAE/Unanticipated Problem Form is received in the IRB office, the IRB Administrator will assign a number to each report, file it in the appropriate study's file, and enter the report into the SAE database.

At each convened meeting, the IRB will review all new SAE and unanticipated problem reports and select one of the following actions:

1. Determine the relationship of the SAE/unanticipated problem to the protocol (not related, possibly related, or definitely related),
2. Request additional information regarding the SAE or problem from the PI, or
3. Determine whether a secondary review of the SAE or problem is necessary by an outside reviewer.

For SAEs and unanticipated problems which require a secondary review, the IRB Administrator will forward copies of the reports to the Medical Director for review. If the Medical Director is a researcher on the study, they will be sent to an External Reviewer for the specific study. The Medical Director/External Reviewer will review the report and may ask for additional information from the investigators, such as hospital records, death certificates, pathology or autopsy reports, or request that it be reviewed by another reviewer, if necessary. If external documents such as hospital discharge summaries are not received by the IRB office within 90 days of initial request, SAE reviewers shall complete their report

based on available information. Should additional information later become available, the report may be re-opened for review. The reviewer will determine, to the best of his/her abilities, whether the SAE's relationship to the study is possibly related, definitely related, or not related.

The IRB Administrator will contact the investigator if the IRB or Medical Director/External Reviewer requires more information, or if any protocol or consent form changes have been requested.

Follow-up reports and correspondence from investigators and Reviewers will be reviewed at a convened meeting. If protocol or consent form changes have been recommended by either the investigator or the Reviewer, the IRB will make the decision to accept/reject these proposed changes or to require new ones. The IRB may require more frequent review to monitor the protocol. In rare instances it may become obvious to the Chairperson and the Board that a study carries an unacceptable, unanticipated risk, and the investigator may be asked voluntarily to suspend the study, if he or she has not already done so, pending its re-evaluation. If the problem is deemed of sufficient magnitude, the IRB will direct the IRB Office to promptly report the injury or unanticipated problem involving risks to subjects to the appropriate institutional officials, OHRP, and any other sponsoring Federal department or agency.

SAEs Involving a Death, Life-Threatening Event, or Serious Breach of Human Participant Protections

The IRB Administrator will immediately inform the IRB Chairperson, Institutional Official, and Medical Director of SAEs involving a death, life-threatening event, or serious breach of human participant protections. The IRB Chairperson may decide to call a special IRB meeting to review the SAE and determine whether to modify the protocol and/or the consent form, suspend the study, or take other appropriate action. The Institutional Official will contact the President of FRI's Board of Directors and they will decide whether to notify all Board members prior to the next scheduled meeting.

The IRB is aware that research investigators are not always successful in obtaining participants' death certificates, as they are not legally entitled to them. However, investigators should attempt to obtain death certificates. If a death certificate cannot be obtained and there is little to no chance that the death could be related, the IRB will administratively close the review of the SAE.

Routine Reports of SAEs

The Institutional Official (or his/her designee) will report a summary of SAEs and any related actions to the Board at its quarterly meetings.

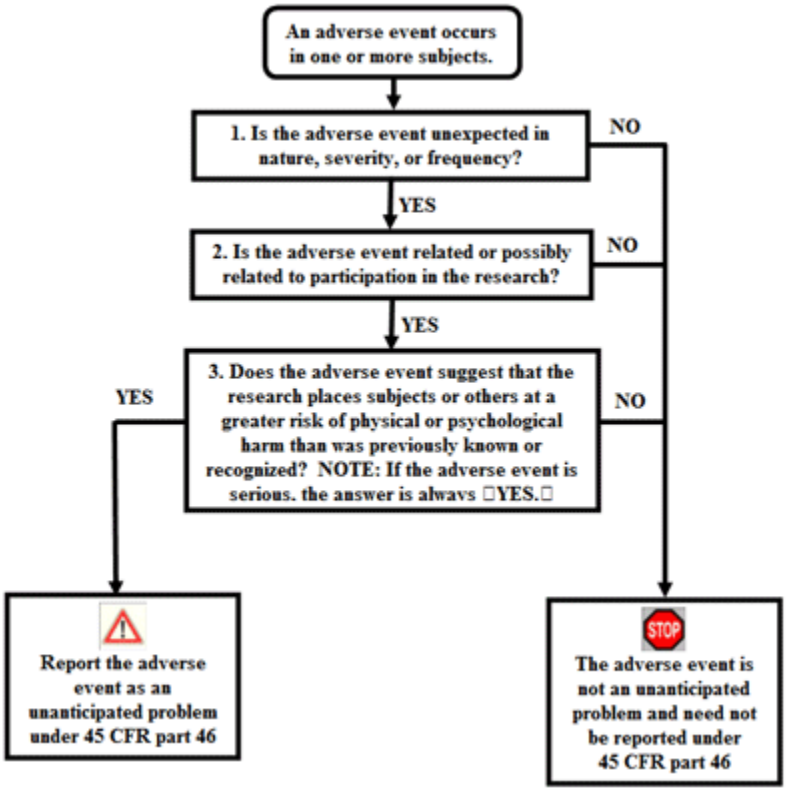
Reporting Requirements to External Agencies

In accordance with 46.103(b)(5), the IRB Administrator will ensure <u>prompt</u> reporting of the following to the IRB and FRI's Institutional Official:

1. Any unanticipated problems involving risks to participants or others,
2. Any serious or continuing noncompliance with the Federal regulations (45 CFR 46) for the protection of human subjects, or the requirements, and determinations of the IRB, and
3. Any suspension or termination of IRB approval

Unanticipated problems occurring in research covered by an OHRP-approved assurance also must be reported by the institution to the supporting HHS agency head (or designee) and OHRP (45 CFR 46.103(a)).

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR part 46.



The Institutional Official will report unanticipated problems to FRI's Board of Directors, the OHRP, and the FDA (if appropriate).

IRB staff will send correspondence, which fulfills FRI's external reporting requirements via Federal Express, United Parcel Service, or another similar overnight carrier which can track the report and verify receipt of the documents.

Additional Adverse Event Reporting Requirements

Investigators are also responsible for reporting the following to the IRB in a timely fashion.

1. New information that may impact the risk/benefit ratio of a study: This may include research findings from other studies, new information in the literature, new FDA labeling and alerts, etc. After careful review, the IRB may recommend that the PI revise the consent form and/or protocol, or change the approval status of the study or the time-frame for continuing review.

2. Irregularities in conducting the study: Examples include study enrollment prior to obtaining informed consent, improper recruitment (e.g., through coercion), protocol changes implemented without IRB approval, administering a study medication prior to obtaining written consent, administering incorrect dosage of study medication (regardless of injury), and the improper use of study equipment or devices (regardless of any injury).

3. Data and Safety Monitoring Board reports: as soon as they are available

4. Copies of external SAEs: sent to the PI from the sponsor or other investigators for multi-site studies.

Applicable Regulations and Guidelines

45 CFR 46.103(b)(5)
45 CFR 46.103(a)
OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 15, 2007)
Guidance on Reporting Incidents to OHRP (June 20, 2011)
FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subjects Protection (January 2009)
21 CFR 56.108(b)(1)
21 CFR 312.66
21 CFR 312.53(c)(1)(vii)