

ADVERSE EVENT
IRB GUIDELINES - REPORTING OF UNANTICIPATED PROBLEMS INVOLVING RISKS TO PARTICIPANTS OR OTHERS

Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that investigators promptly report "any unanticipated problems in involving risk to subjects or others."

- 45 CFR 46 Sec 103 (b)(5)

Institutions must have "Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval."

- 21 CFR 56 Sec 108 (b)

Institutions must have "written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drugs Administration of: (1) Any unanticipated problems involving risks to human subjects or others....."

An Adverse Event (AE) is an unanticipated problem involving "risk" to subjects that ultimately results in harm to the subject (impacts on subjects morbidity and mortality) or others. AE reports must be filed with the sponsor and the Institutional Review Board (IRB) when any of the following happens to a subject on a study:

1. Death
2. Unanticipated "risk" requiring treatment, hospitalization or prolongation of existing hospital stay
3. Any suspicious findings that may have relationship to the study
4. Adverse pregnancy outcome before, during and at the time of delivery
5. Birth defects or congenital anomaly
6. Loss of research records that contain identifiable information
7. Overdose of drug
8. Unusual frequency or intensity of expected effects described in the informed consent document or trends in one type of AE event toward within a protocol (serious or not)
9. Breach of confidentiality
10. Unanticipated problems involving risks to "others" (Example: A nurse in a research study is inadvertently stuck by a needle containing a chemotherapeutic agent that is teratogenic, mutogenic, etc)
11. Abnormal test results that is critical to evaluate the "risk" or "safety" of subjects
12. Unexpected – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process.
13. Unanticipated Adverse Device Effect (ADE) means any serious adverse effect on health and safety of any life-threatening problem or death caused by or associated with a device, if that effect, problem or death was not previously identified in:

- a. Nature

- b. Severity
- c. Degree of incidence in the:
 - i. In the investigational plan or application
 - ii. Supplementary plan or application
 - iii. Any other unanticipated serious problem associated with the device that relates to the:
 - 1. Rights
 - 2. Safety
 - 3. Welfare of subjects

A. Definitions

1. Adverse Event: Any untoward physical or psychological occurrence or undesirable and unintended effect for a participant that may present itself during interventions and interactions used in the research or the collection of identifiable private information under the research, regardless of whether there may or may not be a relationship with the research intervention.

2. Expected adverse event: An adverse event that is not an unexpected adverse event.

3. Unexpected adverse event: Any adverse event, the specificity, frequency or severity of which is not consistent with either:

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

b. the expected natural progression of any underlying disease or condition of the participant(s) experiencing the adverse event.

4. Related to the research: An event is related to the research if, in the opinion of the University of North Alabama investigator, it was more likely than not to be the result of the interventions and interactions used in the research or the collection of identifiable private information in the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

5. Unrelated to the research: An adverse event is unrelated to the research if, in the opinion of the UNA investigator, the adverse event is not related to the research.

6. Internal events: Adverse events experienced by participants enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

7. External events: Adverse events experienced by participants enrolled in multicenter clinical trials at sites other than the site(s) over which the IRB has jurisdiction.

8. Unanticipated problems involving risks to participants or others (unanticipated problems): Problems that are (1) unexpected (in terms of nature, severity or frequency) given the research procedures and the participant population being studied; and (2) suggest that the research places participants or others at a greater risk of harm or discomfort related to the research than was previously known or recognized including physical, psychological, economic or social harm.

B. IRB Reporting Requirements

1. Investigators are required to promptly report the following problems to the IRB:

a. Adverse events that are (1) unexpected and (2) related or likely related to the research as determined by the UNA principal investigator;

b. Information that indicates a change to the risks or potential benefits of the research. For example:

- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
- A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB;

c. Breach of confidentiality;

d. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;

e. Incarceration of a participant in a protocol not approved to enroll prisoners;

f. Specific protocol-defined events that requires prompt reporting to the sponsor;

g. Sponsor imposed suspension for risk;

h. Accidental or unintentional deviations to the IRB-approved protocol that involved risks;

i. Emergency protocol deviations taken without prior IRB review to eliminate apparent immediate hazard to research participants;

j. Complaints of participants that indicate unanticipated risk or which cannot be resolved by the research staff.

2. Investigators must report problems to the IRB in accordance with the following timelines:

- a. Internal problems that require prompt reporting and are fatal or life-threatening must be reported to the IRB within one weekday of the principal investigator becoming aware of the problem.
- b. All other internal problems that require prompt reporting must be reported within 5 weekdays of the principal investigator becoming aware of the event or problem.
- c. External problems that require prompt reporting are to be reported within 30 days of their receipt by the UNA principal investigator.

3. Reports must include the following:

- a. An Unanticipated Problem Report Form, (Appendix A), which includes identifying information (title of the research, name of principal investigator, and name of the sponsor), and a description of the event;
- b. Any associated materials, if any, such as medical record notations, forms sent to a sponsor or the sponsor's safety report forms.

4. Records for problems and adverse events that do not require prompt reporting:

- a. For internal adverse events that are expected and related and are consistent with the frequency and severity listed in the informed consent document, the principal investigator keeps a summary of the events that have occurred within the last approval period and submits the summary at the time of continuing review using the Event Tracking Log (Appendix C) .
- b. Accidental or unintentional deviations to the IRB-approved protocol that do not involve risks to participants may be submitted to the IRB using the Protocol Deviation/Violation Report Form (Appendix B) if required by the sponsor.
- c. External adverse event reports that do not require prompt reporting to the IRB, are reviewed, initialed and dated by the principal investigator and filed with the research regulatory documents. This record is to be made available to the IRB upon request.

C. IRB Process for Handling Reported Problems

- 1. All reports are provided to an IRB Administrator for review within five working days of their receipt.
- 2. The IRB Administrator reviews the materials to determine if the report includes the necessary information and for an initial evaluation.
 - a. If the report is incomplete, it is returned to the investigator with a request for the additional information.

- The UNA principal investigator's assessment of external events must be provided or the report will be considered incomplete and will be returned to the investigator.

b. If in the judgment of the reviewer, the report is definitely not an unanticipated problem involving risks to participants or others, the following procedures are followed:

- If the report is for an external adverse event, the report is returned to the investigator with an explanation for why it is being returned.
- If the report is for an internal event, the report is accepted, signed by the reviewer and filed in the IRB study file. A correction to the log will be requested.
- If the report is for a publication, safety monitoring report, interim results, or other findings, the report is accepted, signed by the reviewer and filed in the IRB study file.

c. All other reports are referred to the full IRB for further action with the following exceptions.

d. If, in the judgment of the reviewer, participants may be at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, an IRB Chair, or the Director of Sponsored Programs is consulted. If the Chair or a Director determines that participants are at immediate risk of harm, the principal investigator will be required to suspend the study according to IRB policy for suspension or termination of research.

3. For reports that are sent to the full IRB for review, the report is added to an IRB meeting agenda and is assigned to a primary reviewer by the IRB staff on the basis of the scientific expertise of the review. The primary reviewer and all other board members receive the following information:

- a. A copy of the report;
- b. A copy of all supplemental material attached to the report;
- c. A copy of all tracking logs, if applicable;
- d. A copy of the sponsor adverse event report form, if applicable;
- e. A summary of the study;
- f. Copies of the current, IRB-approved informed consent document(s) and revised informed consent document(s); and
- g. Any other relevant materials.

4. The primary reviewer summarizes the report at the convened IRB meeting and the full IRB will determine if the report meets the definition of an unanticipated problem involving risks to participants or others by deciding if the event meets the following criteria:

a. Unexpected, i.e., not anticipated (in terms of nature, severity or frequency) given the research procedures and the participant population being studied; and

b. Places participants or others at a greater risk of harm or discomfort related to the research than was previously known or recognized including physical, psychological, economic or social harm.

5. The IRB may decide to postpone a decision while awaiting additional information. If, in the judgment of the IRB, participants may be at immediate risk of harm while waiting for this information, the principal investigator may be required to suspend the study according to IRB policy for suspension or termination of research.

6. If the IRB determines that the event meets both criteria, then the event will be considered an unanticipated problem involving risk to participants or others and will be processed as follows:

a. The IRB will consider the following actions:

- No action necessary;
- Modification to the protocol;
- Modification to the informed consent document(s) for future participants;
- Notification of current or past participants by phone, letter or addendum to the informed consent document;
- Modification of the continuing review schedule;
- Monitoring of the research or consent process;
- Referral to legal counsel, risk management or the institutional official; or
- Other appropriate action as determined by the IRB.

b. For a report of an accidental or unintentional deviation to the IRB-approved protocol that involved risks or has the potential to recur, the IRB will also consider if the event represents serious or continuing non-compliance.

c. For a report of an emergency protocol deviation taken without prior IRB review, the IRB will consider if the changes were consistent with the rights and welfare of participants.

d. The IRB decision and required actions are documented using the appropriate template and this documentation is sent to the principal investigator.

e. The IRB submits a report of the unanticipated problem involving risk to participants or others to appropriate institutional officials and entities.

7. If the IRB determines that the reported event or information does not meet one of the two criteria, then the event or information will not be considered an unanticipated problem involving risk to participants or others; therefore, no further action is required. The IRB decision is documented using the appropriate template and this documentation is sent to the principal investigator.

8. Investigators may appeal the IRB determinations regarding the report of an unanticipated problem involving risks to participants or others. In order to appeal an IRB decision, the investigator must submit his/her rationale or that of the sponsor and any supporting information. An appeal must be reviewed by the IRB that made the original decision.

D. IRB Process for Handling Non-Reported Events

1. Internal events submitted on the Event Tracking Log will be reviewed at the time of continuing review.

2. Accidental or unintentional deviations to the IRB-approved protocol that do not involve risks are reviewed by an IRB Administrator.

a. If the report is incomplete, it is returned to the investigator with a request for the additional information.

b. If the investigator indicates that the deviation involved risks, the IRB Administrator contacts the investigator to request that the investigator complete the Unanticipated Problem Report Form.

c. Otherwise, the IRB Administrator stamps the form acknowledging receipt by the IRB Chair, signs, dates the form and returns a copy of the form to the investigator.

3. External events submitted to the IRB are reviewed by an IRB Administrator.

a. If the report is incomplete, it is returned to the investigator with a request for the additional information.

b. If the investigator indicates that any event meets the definition of a reportable problem, the IRB Administrator contacts the investigator to request that the investigator complete the Unanticipated Problem Report Form.

c. Otherwise, the IRB Administrator stamps the form acknowledging receipt by the IRB office, signs, dates the form and returns a copy of the form to the investigator.

Appendix A
UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS OR OTHERS
PROBLEM REPORT FORM

TITLE OF STUDY:	CURRENT DATE:
SPONSOR	OGCA # (IF APPLICABLE)

PRINCIPAL INVESTIGATOR:	
University Status (Faculty, Staff, Post-doc.):	Telephone Number:
Email Address:	Dept.:

COORDINATOR/CONTACT:	
University Status (Faculty, Staff, Student, etc.):	Telephone Number:
Email Address:	Dept:

1. Indicate the type of event/problem:
- ☐ Adverse event that is: (1) unexpected and (2) related/likely related to the research as determined by the principal investigator.
 - ☐ Specific protocol-defined events that require prompt reporting to the sponsor
 - ☐ Breach of confidentiality
 - ☐ Incarceration of a participant in a protocol not approved to enroll prisoners
 - ☐ An accidental or unintentional deviation to the IRB-approved protocol that involved risks
 - ☐ An emergency protocol deviation taken without prior IRB review to eliminate an apparent immediate hazard to a research participant
 - ☐ A complaint of a participant that indicates an unanticipated risk or any complaint that cannot be resolved by the research staff
 - ☐ Information that indicates a change to the risks or potential benefits of the research. For example,
 - An interim analysis or safety monitoring report indicating that frequency or magnitude of harms or benefits may be different than initially presented to the IRB; **OR**
 - A paper published from another study indicating that the risks or potential benefits of the research may be different than initially presented to the IRB.
 - ☐ Change in FDA labeling or withdrawal from marketing of the study drug, device or biologic used in this research protocol
 - ☐ Sponsor imposed suspension for risk

2. Location of event:

- ☐ At University of North Alabama campus.
- ☐ At another site in a multicenter study in the protocol of report
- ☐ Other → Explain:

3. Is the study permanently closed to enrollment?

- ☐ Yes
- ☐ No

4. Is anyone at this site still on study treatment (drugs, device, intervention)?

- ☐ Yes
- ☐ No

5. Indicate the type of report:

- ☐ Initial report
- ☐ Follow-up report

6. Date of problem/event:

7. Date of discovery of problem/event, if applicable:

8. Identify drug, biologic, device, treatment, intervention, etc., if applicable:

9. Briefly describe the problem/event:

10. Has the same problem/event occurred previously in this study?

- ☐ No
- ☐ Yes → What is the number of times this event has occurred study-wide?

11. Is the problem/event ongoing?

- ☐ Yes
- ☐ No

↳ Date the problem/event ended.

↳ Outcome of the problem/event (Check all that apply)

- ☐ Participant was not adversely affected by the problem/event
- ☐ Resulted in prolonged hospitalization
- ☐ Resulted in permanent disability
- ☐ Resolved spontaneously
- ☐ Resolved with treatment
- ☐ Participant discontinued study intervention
- ☐ Participant withdrew from the study
- ☐ Other → Specify. If problem involved breach of confidentiality, please specify the nature of data involved:

12. Are the specificity, frequency and severity of this problem/event consistent with the study and consent document?

- ☐ Yes
- ☐ No → Explain why not:

13. Based on your analysis of this event, should the consent document be revised?
- ☐ No
- ☐ Yes → Submit a revised consent document and a *Request for Modification* letter with this report.
14. Based on your analysis of this event, should the protocol be revised?
- ☐ No
- ☐ Yes → Submit a revised protocol and a *Request for Modification* letter with this report.
15. Based on your analysis of this event, should the research be suspended or terminated?
- ☐ No
- ☐ Yes → Describe the procedures for orderly suspension or termination of the research.
16. Should currently enrolled participants be notified about this problem/event?
- ☐ No
- ☐ Yes → Explain how they will be notified. If an addendum to the consent document will be used, submit this document and a *Request for Modification* letter with this report.
17. Should past participants be notified about this problem/event?
- ☐ No
- ☐ Yes → Explain how they will be notified. If an addendum to the consent document will be used, submit this document and a *Request for Modification* letter with this report.

Comments:

Principal Investigator Certification: My signature certifies that all necessary information has been assessed and the risk-to-benefit ration continues to be acceptable.

Principal Investigator's Signature

Date

Submit to Office of Sponsored Programs.

For Committee Use Only

____ Report Acknowledged/accepted without recommendation.

____ Report Acknowledged/accepted pending receipt of additional information to be submitted to the IRB.

____ Protocol requires full review (disseminate all UP/AE materials to each IRB member).

Comments:

Committee Review Signature _____ Date _____

Appendix B
PROTOCOL DEVIATION/VIOLATION REPORT FORM

The IRB requires reporting of all protocol deviations and/or protocol violations within five (5) business days as per IRB Policy.

1. Deviations generally do not have a major impact on subject welfare or data integrity. Examples of a protocol deviation may include:

- Scheduling a required procedure outside of the time frame specified in the protocol
- Failure of subject to return study medication
- Implementation of unapproved recruitment procedure

2. Violations affect a subjects rights, safety or well-being or integrity of the data being collected. It may also affect the primary safety or efficacy endpoints of the study. Examples are:

- Enrolling subjects who did not meet entry criteria without prior permission
- Failing to obtain informed consent prior to any study-related procedures
- Failure to treat subjects according to protocol procedures that specifically relate to primary safety or efficacy endpoints.

Date: _____

Date of Event: _____

PI Name: _____

Protocol Title: _____

Subject's Initials: _____ **Subjects Study #:** _____ **Subjects Record #:** _____

If externally funded, was the sponsor notified of the protocol deviation/violation?:

Yes ☐ **Date Notified:** _____ No ☐ N/A ☐

Provide a full description of the protocol deviation/violation as well as why the deviation/violation occurred (Attach as many pages as necessary):

What will be done in the future to prevent recurrence of this protocol deviation/violation? (Attach as many pages as necessary)

Submit to: Office of Sponsored Programs, ATTN: Director

Appendix C
INSTITUTIONAL REVIEW BOARD
UNIVERSITY OF NORTH ALABAMA

EVENT TRACKING LOG

Mild or Moderate events related or possibly related i.e., all events that do not meet the criteria for a significant adverse event. See IRB Guidelines - Adverse Events

To provide a history of known *Events* for this protocol, please maintain an accumulative Non-significant Adverse Event Tracking Log. Using this form, these event should be reported to the IRB with the yearly Continuing Progress Report and at the close of the study.

Note: In an effort to monitor trends, please report trends to the IRB as soon as they are noted for projects located at UNA and other study sites if applicable.

Principal Investigator: _____

Project Title: _____

Date of Event	Participant s Identifying No./Initials	Describe EVENT	Magnitude Mild Moderate	Expected/ Unexpecte d	Investigator's Conclusions	Date PI Notified	Entry completed by:

Date _____

PI Signature* _____

Attach additional pages as needed.

*Signature indicates that the PI has reviewed the list and determined that it does not meet the IRB's prompt reporting requirements.

