



Policy Name: Unanticipated Problems and Adverse Events Policy and Procedures			
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I. POLICY

A. Introduction

The purpose of this policy is to define the policies and procedures of MUSC for addressing unanticipated problems involving risks to research participants or others.

II. COMPOSITION OF THE POLICY AND PROCEDURE

A. Description

1. unanticipated problem
2. adverse event
 - a) reportable internal adverse event
 - b) reportable external adverse event
3. unanticipated problem resulting in social, economic or “other” harm

B. Events

1. Unanticipated Problem: Reportable Adverse Event
2. Unanticipated Problem: Reportable Social, Economic or “Other” Harm and/or Increased Risk of Harm to Subjects and Others

III. DESCRIPTION

A. An *unanticipated problem* involving risks to subjects or others is **Any** incident, experience, or outcome meeting **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, i.e. greater than 50% probability to subject’s participation 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) related to the research than was previously know or recognized.

The event may be biomedical, i.e. an adverse event, and/or social behavioral, i.e. an unanticipated problem including privacy/confidentiality issues.

Note: "Harm" does not need to occur for an event to be an unanticipated problem; an unanticipated problem places subjects or others at increased risk of harm.

Source: Office of Human Research Protections (OHRP), DHHS, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007.

Determining whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research may be difficult. When making this assessment, the investigator should take into consideration whether substantive changes in the research protocol or informed consent document, or other corrective actions may be warranted in order to protect the safety, welfare, or rights of subjects or others. Generally, if the problem is considered an unanticipated problem involving risks to subjects, substantive changes to the protocol and/or consent form may be warranted.

- B.** An **adverse event** involves any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research.

A reportable internal adverse event is:

- 1) *unanticipated = not identified in nature, frequency, or severity in the current protocol, informed consent, investigator brochure, or other protocol specific risk information;
- 2) **related or possibly related to participation in research = there is a reasonable possibility, i.e. 50% or greater, the event may have been caused by participation in the research; **and**
- 3) ***serious =
 - a. Death;
 - b. Life threatening;
 - c. Inpatient hospitalization or prolonged existing hospitalization;
 - d. Persistent or significant disability/incapacity;
 - e. Cancer;
 - f. Overdose; or
 - g. Congenital anomaly/birth defect or is more prevalent than expected or the event suggests that subjects or others are at

greater risk of physical or psychological harm than previously recognized (21 CFR 312.32).

See <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>, appendices C and D, for examples of reportable and non reportable adverse events.

A reportable external adverse event is determined by a Data Safety Monitoring Board (DSMB) or a Central Monitoring Entity (CME) to be:

- a. Unanticipated;
- b. Related or possibly related to participation in research;
- c. Serious or more prevalent than expected; and
- d. The DSMB/CME recommends a specific change to the protocol/informed consent based on the event, for example, modification of inclusion/exclusion criteria, and revision of the informed consent to encompass newly identified risks.

C. An **unanticipated problem** resulting in social, economic, or “other” harm or increased risk of harm to subjects or others is:

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 subject’s participation in the research;
3. Suggests that the research places subjects or others at a greater risk of harm (including psychological, economic, or social harm) related to the research than was previously known or recognized and
4. Must be reported.

Examples of incidents, experiences, or outcomes that may meet the definition of unanticipated problems involving risks to subjects or others include:

- a. Participant complaints;
- b. Laboratory errors;
- c. Medication errors;
- d. Procedural errors;
- e. Unauthorized disclosure of confidential information;

- f. Lost or stolen confidential information;
- g. Disqualification of investigators; or
- h. Suspension of investigators.

(OHRP, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007). For additional examples of unanticipated problems that do not involve adverse events and need to be reported under the HHS regulations at 45 CFR 46, see <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>, appendix B.

IV. UNANTICIPATED PROBLEM : REPORTABLE ADVERSE EVENT

A. Policy

1. Reportable adverse events that are “alarming”, i.e. fatal or immediately life threatening, are to be reported immediately to the sponsor and the IRB [21 CFR 312.64(b)].

FATAL - INTERNAL: All deaths, during a study or within 30 days post termination from a study, regardless of cause, are to be reported online to the IRB.

FATAL - EXTERNAL: All deaths, during a study or within 30 days post termination from a study only if they meet reportable criteria above.

2. Reportable adverse events other than those that are “alarming” are to be reported online to the IRB as soon as possible but no later than 10 working days after the investigator first learns of the event. Changes made in the approved research to eliminate immediate harm to subjects must be reported within 24 hours.
3. If a reportable adverse event is reported later than 10 working days after awareness of the event, an explanation of the deviation from policy must accompany the reported event.
4. The principal investigator is responsible for information from study sponsors. Therefore, the principal investigator will maintain a copy of all external adverse event reports which are not reportable to the IRB per this policy. This information will include the basis for the determination of an event as an adverse event. The principal investigator’s documented analysis of all external events is subject to review by the IRB or MUSC University Compliance Office.

Note: The IRB will not accept internal or external adverse events which do not meet the MUSC IRB definition of “reportable” adverse events.

B. Procedures for Reporting, Reviewing, and Actions

1. The principal investigator will electronically report an internal adverse event using the Internal Adverse Event Report. If the event is “alarming”, the investigator will call the IRB to alert the chair of the event.
2. The principal investigator will electronically report an external adverse event using the external adverse event report from the sponsor only when an external adverse event meets the MUSC definition of a “reportable adverse event”. The assigned IRB staff will review reported adverse events prior to the IRB Chair review.
3. The Chair, Vice-chair, or designee, will review the electronic report including the protocol changes that already have been made for immediate safety reasons and those proposed and determine if there is a need for immediate action beyond the action taken/recommended by the principal investigator with consultation of the principal investigator. The Chair, Vice-Chair or designee will determine whether the actions taken provide for the continued welfare of all study participants.
4. If the chair or vice chair decides the research immediately should be suspended to enrollment of new subjects or research activities involving currently enrolled subjects should be suspended given the nature of the adverse event, the principal investigator will be notified in writing of the decision and actions to be taken to protect currently enrolled subjects. The Organizational Official(s) will be notified of a suspension within 24 hours.
5. The adverse event and actions taken by the principal investigator and chair, all proposed changes to the protocol and/or informed consent, and all other pertinent information such as national/international experiences with the research study if available will be reviewed by the Board at a convened meeting. The Board may require additional modifications. These actions may include:
 - a) Revision of the protocol including inclusion/exclusion criteria;
 - b) Incorporation of new information into the informed consent;
 - c) Implementing additional data monitoring activities;
 - d) Informing currently enrolled participants;
 - e) Suspension of enrollment of new subjects;
 - f) Suspension of research procedures in currently enrolled subjects; and/or

- g) Notifying previously enrolled subjects of the event and any actions they should take (OHRP, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007).
- 6. If the Board requires additional modifications, the principal investigator will be notified in writing of these changes with a request that these requirements be submitted for IRB review after discussion with the study's sponsor.
- 7. The IRB chair will submit a written report to the Organizational Official(s) / VAMC Institutional Official (if applicable) copied to the principal investigator within 10 working days after review of the event by the convened Board. This report will include:
 - a) The name of the institution;
 - b) Title of the research study;
 - c) The name of the principal investigator;
 - d) Number assigned by the IRB and any numbers assigned by another agency/sponsor;
 - e) The IND or IDE number if applicable;
 - f) A detailed description of the adverse event; and
 - g) Actions the principal investigator and the IRB have taken or will implement to address the problem and prevent future occurrences.
- 8. The Organizational Official(s) will review the event and discuss the report with the IRB chair and the Director of the Office of Research Integrity. The Organizational Official will notify OHRP, the FDA if appropriate, the sponsor, and other agency officials as appropriate within 10 working days of receiving the Chair's report regarding the adverse event or unanticipated problem including those resulting in IRB suspension or termination of the protocol.
- 9. If the research study is a VA protocol, the following will be notified
 - 1) The Associate Chief of Staff/Research & Development
 - 2) the VA Privacy Office (when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information). VA policy for reporting to the VA Office of Research Oversight will be followed.

V. UNANTICIPATED PROBLEM: REPORTABLE SOCIAL, ECONOMIC OR "OTHER" HARM AND/OR INCREASED RISK OF HARM TO SUBJECTS AND OTHERS

A. Policy

1. An unanticipated problem resulting in social, economic or “other” harm or increased risk of harm should be reported to the IRB as soon as possible but no later than 10 working days after the investigator first learns of the event. Changes made in the approved research to eliminate immediate harm to subjects must be reported within 24 hours.
2. The Chair, Vice- chair, or designee will review the report including the protocol changes already implemented for immediate safety reasons and those proposed and determine if there is a need for immediate action beyond the action taken/recommended by the principal investigator.
3. If an unanticipated problem is reported later than 10 working days after awareness of the event, an explanation of the deviation from policy must accompany the reported event.

B. Procedures

1. The principal investigator will submit a written report to the IRB which will include at a minimum:
 - a) the name and HR number of the protocol;
 - b) a detailed description of the incident/event;
 - c) an explanation of the basis for determining that the incident/event involving risks to participants or others represents an unanticipated problem; and
 - d) a description of any changes to the protocol to eliminate immediate harm to subjects and other modifications that have been taken or are proposed in response to the unanticipated problem

(OHRP, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007).
2. The assigned IRB staff will review any unanticipated problem reports and place the reports and corresponding protocol files in the chair’s office.
3. The chair, vice chair, or designee, will review the report including the protocol, informed consent documents, changes already implemented for immediate safety reasons and those proposed and determine in consultation with the principal investigator if there is a need for immediate action beyond the action taken/recommended by the principal investigator.

4. If the chair or vice chair decides the research should be suspended to enrollment of new subjects or research activities involving currently enrolled subjects should be suspended given the nature of the unanticipated problem, the principal investigator will be notified in writing of the decision and actions to be taken to protect currently enrolled subjects.

5. The unanticipated problem, actions taken by the principal investigator and chair, all proposed changes to the protocol and/or informed consent, and all other pertinent information such as national/international experiences with the research study if available will be reviewed by the Board at a convened meeting. The Board may require additional actions. These actions may include:
 - a) revision of the protocol including inclusion/exclusion criteria;
 - b) incorporation of new information into the informed consent;
 - c) implementing additional data monitoring activities;
 - d) informing currently enrolled participants;
 - e) suspension of enrollment of new subjects;
 - f) suspension of research procedures in currently enrolled subjects;
 - g) notifying previously enrolled subjects of the event and any actions they should take;
 - h) termination of the research; and/or
 - i) notification to current participants when such information may relate to participants' willingness to continue to take part in the research.

(OHRP, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007). The Board's discussion and required actions will be documented in the IRB minutes.

6. If the Board requires additional actions, the principal investigator will be notified in writing of these changes with a request that these modifications be submitted for IRB review after discussion with the study's sponsor.

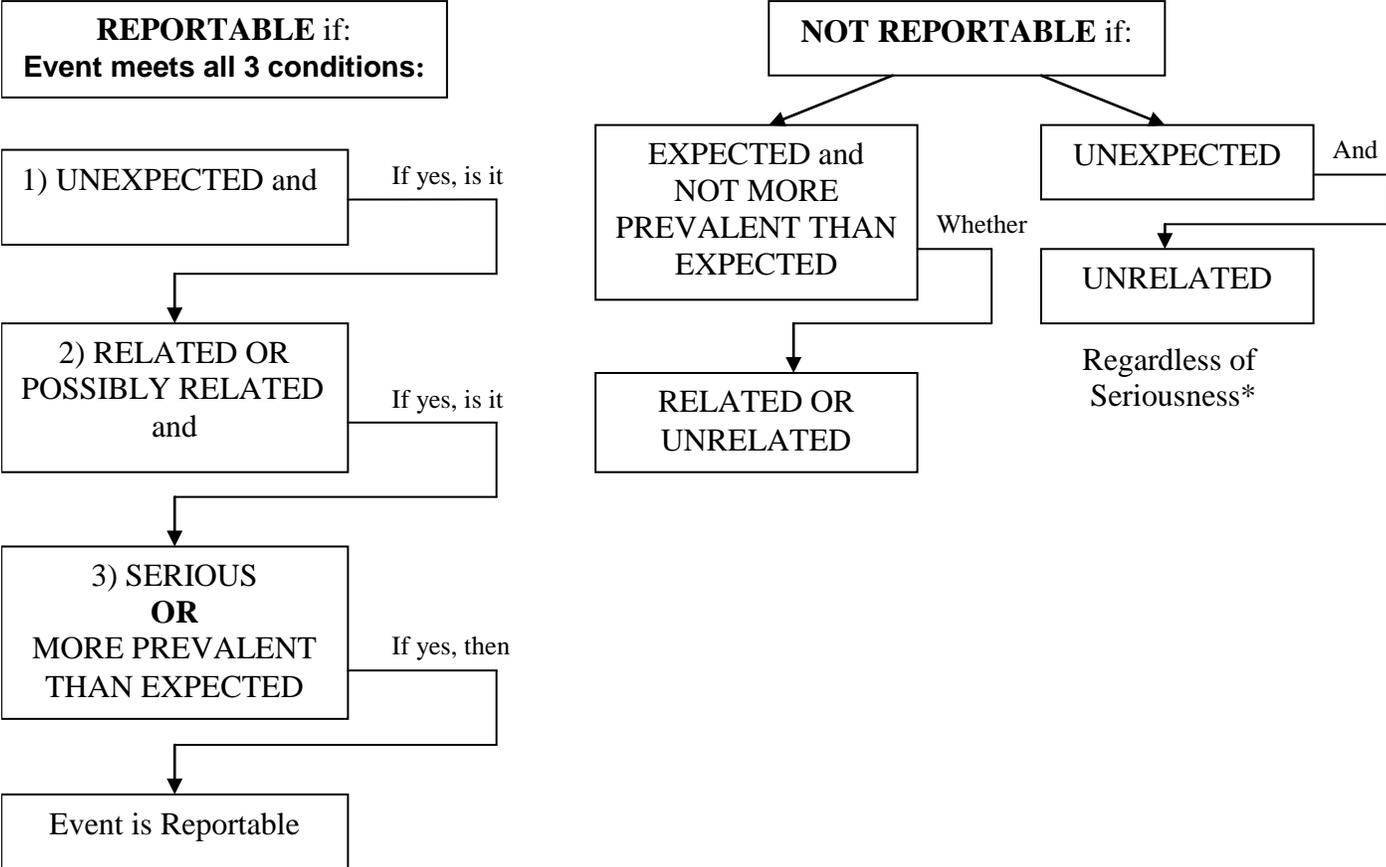
7. The Chair will submit a written report to the Organizational Official(s) copied to the principal investigator within 10 working days after review of the event by the convened Board. This report will include:
 - a) the name of the institution;
 - b) title of the research study;

- c) the name of the principal investigator;
 - d) number assigned by the IRB and any numbers assigned by another agency/sponsor;
 - e) the IND or IDE number if applicable;
 - f) a detailed description of the unanticipated problem; and
 - g) actions the principal investigator and the IRB have taken or will implement to address the problem and prevent future occurrences.
8. The Organizational Official(s) will review the event and discuss the report with the IRB chair and the Director of the Office of Research Integrity. The Organizational Official will notify OHRP, the FDA if appropriate, the sponsor, and other agency officials as appropriate within 10 working days of receiving the Chair's report regarding the unanticipated problem including those resulting in IRB suspension or termination of the protocol.
9. If the research study is a VA protocol, the following will be notified
1) The Associate Chief of Staff/Research & Development 2) the VA Privacy Office (when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information). VA policy for reporting to the VA Office of Research Oversight will be followed.

VI. REFERENCES

- A. [Office of Human Research Protections \(OHRP\), DHHS, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007.](#)
- B. Reportable Event Flowcharts (following page)

Reporting Requirements for INTERNAL Adverse Events



***Reporting Requirements for INTERNAL DEATHS**

All internal deaths
during the study or 30 days post termination from protocol, are required to be reported as adverse events even if they are expected or unrelated.