



Policy Name: Unanticipated Problems and Adverse Events Policy and Procedures		
Approved		
Effective Date: 08/01/2012	Page 1 of 9	Section: HRPP 4.7
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I. INTRODUCTION

This policy defines the policies and procedures of MUSC for addressing unanticipated problems involving risks to research participants or others (UPIRSOS).

MUSC investigators are required to promptly report to the IRB if there are unanticipated problems during the course of the research that involve risks to subjects or to others. MUSC IRB will not review reports of adverse events, whether at MUSC or external sites, unless those reports constitute unanticipated problems involving risks to subjects or others.

See letter to the research community and sponsors posted at <http://research.musc.edu/ori/irb/docs/Magruder%20Letter%20October%201%202010.pdf>

II. MEMORANDUM OF UNDERSTANDING

In aspects where the MUSC IRB is being utilized by the Ralph H. Johnson VA Medical Center, both parties will abide by the agreements set forth in the current “Memorandum of Understanding Between The Ralph H. Johnson VA Medical Center And The Medical University of South Carolina Concerning Utilization of the Medical University of South Carolina’s Institutional Review Boards”.

III. DEFINITIONS

According to federal guidance, an unanticipated problem involving risks to subjects or others (UPIRSOS) refers to any incident, experience, or outcome that:

- is 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;
- is related or possibly related to a subject’s participation in the research; and

- 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 known or recognized.

Adverse event or adverse experience (AE) is 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, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

- Internal adverse event is an adverse event experienced by subjects enrolled by the investigator(s) at MUSC or at a site for which MUSC has oversight.
- External adverse event is an adverse event experienced by subjects enrolled by investigators at other institutions engaged in a multi-site clinical trial.

Serious Adverse Event (SAE) is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unexpected Adverse Event as defined by the FDA, is any adverse event, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Possibly related to the research refers to the reasonable possibility that the adverse event, incident, experience or outcome may have been associated with the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

Related to the research refers to an incident, experience or outcome that is likely to have resulted from participation in the research study.

IV. DECIDING IF AN EVENT MEETS THE CRITERIA FOR UNANTICIPATED PROBLEM INVOLVING RISK TO SUBJECTS OR OTHERS

A. Is it unexpected?

An event is unexpected if it occurs in one or more subjects or others participating in a research protocol, and the event's nature, severity, or frequency is not consistent with either:

- 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
- 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.

B. Is it related or possibly related to a subject's participation in the research?

Events that are related or possibly related to participation in the research may be caused by one of the following:

- The procedures involved in the research;
- An underlying disease, disorder, or condition of the subject;
- Other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, events that are determined to be at least partially caused by the procedures in a study would be considered related to participation in the research, whereas events determined to be solely caused by the subject's condition or state of illness or other circumstances clearly outside of the study would be considered unrelated to participation in the research

C. Does it suggest that the research places subjects or others at greater risk of harm than was previously known or recognized?

Adverse events that are: 1) unexpected, 2) related or possibly related to participation in research, and 3) serious are the most important subset of adverse events representing unanticipated problems, because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. These events warrant consideration of substantive changes in the research protocol and/or informed consent process/document or other corrective actions in order to protect the safety, welfare or rights of subjects.

If the answers are that the event is a) unexpected, b) related or possibly related and c) serious, it is a UPIRSOS and should be reported to the MUSC IRB.

Other adverse events that are unexpected and related or possibly related to participation in the research, but not serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. These events should also be reported, for consideration of changes or corrective actions.

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. Examples of unanticipated problems that should be reported to the IRB, even though they are not adverse events, include:

- Publication in the literature, safety monitoring report (e.g., DSMB report), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Breach in confidentiality resulting from a disclosure of confidential information or from lost or stolen confidential information, that may involve risk to that individual or others;
- Complaint of a participant or family member that indicates an unanticipated risk;
- Laboratory or medication errors that may involve potential risk to that individual or others;
- Change in FDA labeling because of adverse consequences or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Disqualification or suspension of investigators;
- Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;

- Deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- Any deviation from the IRB-approved protocol that increases the risk or affects the participant's rights, safety, or welfare.

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.

IV. REQUIRED REPORTING OF UNANTICIPATED PROBLEMS

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Investigators must report to the IRB any unanticipated problem involving risk to subjects or others. The reported information must include: a description of the event, the date of occurrence, whether it is a local or outside report, how the event affected the rights, safety or welfare of the subject or others, current status of MUSC subjects, and any planned changes or modifications to the project as a result of the event.

Reports from the investigator to the IRB must be submitted no later than 10 working days after the event or notification to the investigator that the event has occurred.

When a research study includes investigational drugs or devices, some unanticipated problems may also meet the definition of an unexpected adverse drug experience (serious or otherwise), or an unanticipated adverse device effect. MUSC investigators and research staff are expected to be familiar with the various requirements for reporting of adverse events and UPIRSOs.

When a UPIRSO report is filed with IRB, the staff will compare the content of the report with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event appears to meet the definition of an unanticipated problem involving risk to subjects or others. This preliminary determination is forwarded to an expedited IRB reviewer.

The IRB reviews the UPIRSO report by expedited procedures in order to determine whether the criteria for approval under 45 CFR 46.111 and 21 CFR 56.111 are still met. In its review of the UPIRSO report, the IRB may determine that additional safeguards need to be developed within the protocol procedures in order to adequately minimize risks. It may require consent form modifications in order to include additional information about this new risk (already enrolled subjects may or may not need to be provided with this new information). The IRB is also responsible to decide whether the study may continue as it was previously approved given this new information.

When very serious risks of harm or serious harms occur, the IRB may consider suspending its approval of the research as a way of safeguarding the rights and welfare of the subjects.

All reports of unanticipated problems involving risks to subjects or others are filed with the appropriate research study. The investigator will be asked to summarize these reports for the IRB at the time of continuing review.

Adverse Events

FDA regulations and clinical trial agreements require the prompt reporting of Serious Adverse Drug Events and Serious Adverse Device Effects to the Sponsor and to FDA. Sponsors are responsible for reporting these events to investigators at other institutions who are conducting research under the relevant IND or IDE of these events. However, these events only need to be reported to the MUSC IRB (whether they occur at MUSC, or at an external site) when they constitute an unanticipated problem involving risks to subjects or others. While non-UPIRSO adverse events still need to be reported to the Sponsor, who must report them to FDA, they do not need to be reported to the MUSC IRB and the MUSC IRB will not review them. The only exception to this is the requirement that adverse device effects need to be reported by the Sponsor to the IRB. If these constitute UPIRSOs, then the MUSC PI will be required to submit an Adverse Event or UPIRSO report.

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.

Deaths on Study

Investigators are required to report to the IRB any death of an MUSC research subject within 24 hours of learning about the death, unless the death is expected (e.g., due to disease progression).

Anticipated deaths (e.g., due to disease progression) may be reported at the time of continuing review.

V. IRB AND OTHER INSTITUTIONAL RESPONSIBILITIES

The assigned IRB staff will review any unanticipated problem reports and forward them to the IRB Chair, or designee, for review.

The 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. Appropriate institutional officials and federal oversight agencies will be promptly notified when applicable. Preliminary notification may be sent in some cases.

If the Chair, or designee, 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 Chair or designee will have the IRB Staff suspend the study in the system which will issue an automatic notification to the Principal Investigator with actions to be taken to protect currently enrolled subjects.

All of the pertinent information regarding the unanticipated problem will be reviewed by the Board at a convened meeting. This information may include the protocol, informed consent, as well as any proposed changes to these documents and any additional information such as national/international experiences within the research study if available. The Board may require additional actions. These actions may include:

- revision of the protocol including inclusion/exclusion criteria;
- incorporation of new information into the informed consent;
- implementation of additional data monitoring activities;
- informing currently enrolled participants;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- notification of previously enrolled subjects of the event and any actions they should take;
- termination of the research; and/or
- notification to current participants when such information may relate to participants' willingness to continue to take part in the research.

The Board's discussion and required actions will be documented in the IRB minutes.

If the Board requires additional actions, the IRB Staff will enter these into the system for automated notification to the Principal Investigator of these changes with a request that these modifications be submitted for IRB review after discussion with the study's sponsor.

The Chair will submit a written report to the Institutional Official(s) copied to the principal investigator within 10 working days after review of the event by the convened Board. This report will include:

- the name of the institution;
- title of the research study;
- the name of the principal investigator;
- number assigned by the IRB and any numbers assigned by another agency/sponsor;
- the IND or IDE number if applicable;
- a detailed description of the unanticipated problem; and
- actions the principal investigator and the IRB have taken or will implement to address the problem and prevent future occurrences.

The Institutional Official(s) will review the event and discuss the report with the IRB chair and the Director of the Office of Research Integrity. The Institutional Official will promptly notify OHRP, the FDA if appropriate, the sponsor, and other agency officials as appropriate within 30 working days of receiving the Chair's report regarding the unanticipated problem including those resulting in IRB suspension or termination of the protocol.

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). The ACOS-R and VAMC compliance officer will follow the procedures of VAMC Handbook 1058.01 Ralph H. Johnson VAMC SOP 21 "Reporting of Research Events to facility oversight committees and the office of research oversight." Revisions to this SOP will be communicated to the MUSC IRB by the VAMC Compliance Officer and/or VA Liaison.

VI. VA Protocols

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). The ACOS-R and VAMC compliance officer will follow the procedures of VAMC Handbook 1058.01 Ralph H. Johnson VAMC SOP 21 "Reporting of Research Events to facility oversight committees and the office of research oversight." Revisions to this SOP will be communicated to the MUSC IRB by the VAMC Compliance Officer and/or VA Liaison.

- a. The terms "unanticipated" and "unexpected" refer to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

- b.** For serious unanticipated problems involving risks to subjects or others, within five business days of becoming aware of any serious unanticipated problem involving risks to subjects or others in VA research, members of the VA research community are required to ensure that the problem has been reported in writing to the IRB. Serious unanticipated problems involving risks to subjects or others include:
 - i.** Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.
 - ii.** Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death.
 - iii.** Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility's research projects.
 - iv.** Any data monitoring committee, data and safety monitoring board or data and safety monitoring committee report describing a safety problem.
 - v.** Any sponsor analysis describing a safety problem for which action at the VA facility might be warranted.
 - vi.** Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others.
 - vii.** Any problem reflecting a deficiency that substantively compromises the effectiveness of the VA facility's HRPP.

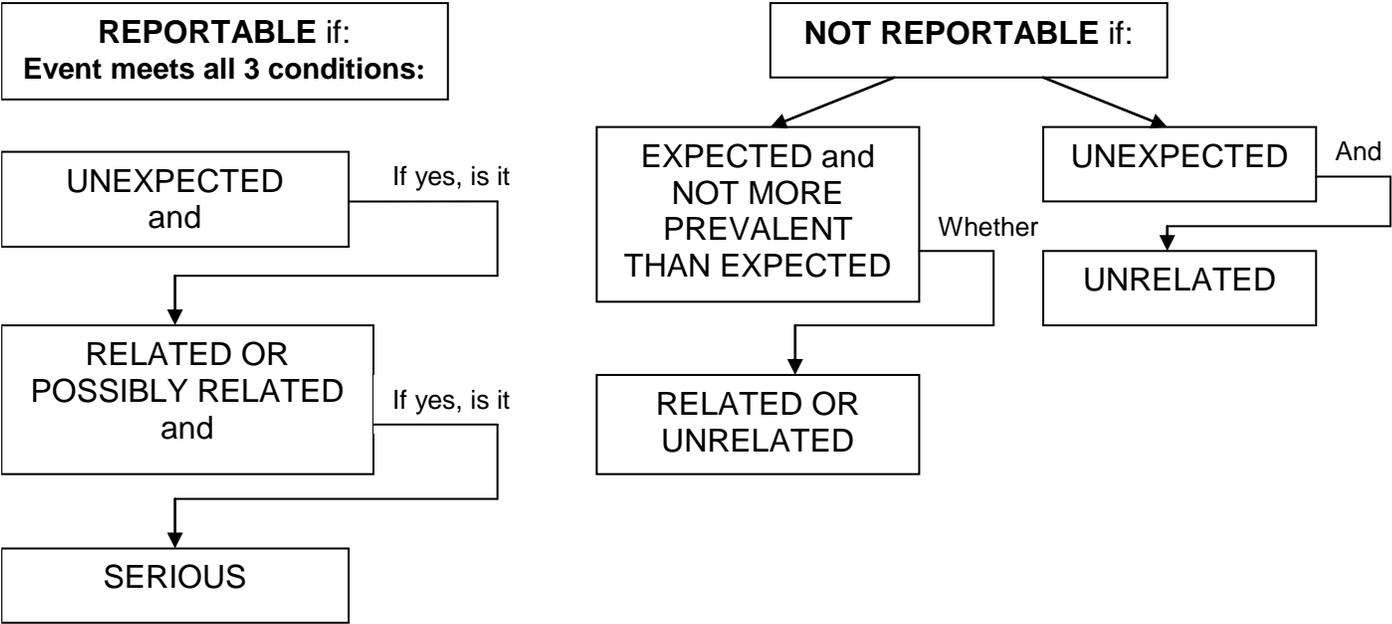
- c.** IRB review of serious unanticipated problems and unanticipated serious adverse events in VA research:
 - i.** Within five business days after a report of a serious unanticipated problem involving risks to subjects or others, or of a local unanticipated serious adverse event, the convened IRB or a the chair or designee must determine and document whether the reported incident was serious and unanticipated and related to the research.
 - ii.** "Related" means the event or problem may reasonably be regarded as caused by, or probably caused by, the research.
 - iii.** If the convened IRB or the IRB chair or designee determines that the problem or event was serious, unanticipated, and related to the research, the IRB chair or designee must report in writing the unanticipated problem or event within five business days after the determination to:

1. Medical center director,
 2. Associate chief of staff for research and
 3. The Research and Development Committee.
- iv. If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, a simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations.
 - v. All determinations of the IRB reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting.
 - vi. If it was determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether a protocol or consent document modification is warranted.
 - vii. If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document:
 1. Whether previously enrolled subjects must be notified of the modification.
 2. When such notification must take place and how such notification must be documented.

VII. 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 study intervention, are
required to be reported as adverse events unless they are expected (i.e.,
due to disease progression).