

Unanticipated Problems Involving Risks to Participants and Others	Effective Date	06.08.07
	Revisions Date	1.15.21

- 1.0 Purpose:** This standard operating practice (SOP) establishes guidelines for prompt reporting of unanticipated problems involving risks to participants or others.
- 2.0 Research Protocols Affected:**
- 2.1** Non-exempt human research (both single site and multi-center) reviewed and approved by the University & Medical Center Institutional Review Board (UMCIRB)
- 2.2** Human research in which an ECU or ECU affiliate’s faculty, staff, or student serves on the research team.
- 3.0 SOP:** This SOP describes the criteria for reporting an unanticipated problem involving risks to participants or others for research that has been reviewed and approved by the UMCIRB. Federal regulations require research institutions to have a prompt method of notifying the Institutional Review Board (IRB), appropriate institutional officials, and appropriate regulatory departments and agencies of these unanticipated problems.

It is important to understand the difference between adverse events and unanticipated problems. Adverse events that do not meet the criteria of being an unanticipated problem should not be reported to the UMCIRB.

- 4.0 Definitions:**
- 4.1** Unanticipated Problems Involving Risks to Participants or Others: any event or outcome that was previously unforeseen and indicates that participants or others are at an increased risk of harm. The Office for Human Research Protections (OHRP) considers unanticipated problems in general to include any incident, experience, or outcome that meets all of the following criteria:
- 4.1.1 unexpected;
 - 4.1.2 related or possibly related to participation in research; and
 - 4.1.3 suggests the research places participants or others at increased risk of harm.
- 4.2** Unexpected event: not previously identified in the investigation plan, protocol, or IRB application (including any supplement, amendment, or subsequent application) that and is unexpected in:
- 4.2.1 nature:
 - 4.2.2 severity: or
 - 4.2.3 degree.
 - 4.2.4 includes but is not limited to:
 - 4.2.4.1 an adverse experience that is more severe or is not specified in the current IRB materials, protocol or investigator brochure; or,
 - 4.2.4.2 is not consistent with the risk information described in the general research plan or current consent document.
 - 4.2.5 Any breaches in confidentiality that would place the participant or others at risk.
 - 4.2.6 Any change in FDA labeling or withdrawal from marketing of a drug, device, or

- biologic used in a research protocol;
- 4.2.7 Any change to the protocol that was taken without prior IRB approval to eliminate apparent immediate hazard to a research participant; or
- 4.2.5 Incarceration of a participant enrolled on a study that was not previously reviewed and approved under the prisoner research provisions. (See SOP for Research Involving Prisoners)
- 4.3. Related or possibly related to participation in research: there is at least a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research. **UMCIRB extends this definition to a minimum of 30 days post-administration of the test article or intervention**
- 4.4 Increased risk of harm: the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- 4.5 Adverse event [or adverse experience (AE)] is any untoward or unfavorable medical occurrence in a participant, including any abnormal sign, symptom, or disease, temporally associated with the individual'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.
 - 4.5.1 Adverse events may be anticipated or unanticipated;
 - 4.5.1.1 An anticipated adverse event may become unanticipated if it occurs more often than expected or if it becomes more pronounced or severe than expected;
 - 4.5.2 Only adverse events that meet the criteria of Unanticipated Problem should be reported to the UMCIRB.

5.0 Responsibilities:

- 5.1 UMCIRB will review unanticipated problems involving risks to participants and others that occur on approved studies to determine whether:
 - 5.1.1 The study poses potentially greater risks than benefits to participants;
 - 5.1.2 The research procedures should be modified to minimize the risk of the event occurring again;
 - 5.1.3 The consent document should be modified to inform potential participants of the risk of the event;
 - 5.1.4 All current and/or previously enrolled participants should be informed of the event through re-consenting;
 - 5.1.5 The study should be suspended until such time that the risks can be minimized;
 - 5.1.6 The study should be terminated, i.e., risks to participants outweigh any potential for benefit that can be gained from participation in the study;
 - 5.1.7 Appropriate actions are needed to protect the welfare and safety of participants based on review of pertinent information; and/or
 - 5.1.8 Additional information is necessary when the event, at the time of reporting, was not resolved, or when additional information is required to make a determination.
- 5.2 University & Medical Center Institutional Review Board (UMCIRB) Administrative Director or designee will

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- 5.2.1 Provide education and resources to investigators and/or study team members regarding their responsibilities to report unanticipated problems;
- 5.2.2 Assist IRB chairperson and IRB members by providing guidance on reviewing unanticipated problems;
- 5.2.3 Compose and send reports to promptly notify the Office for Human Research Protection (OHRP), and other applicable agencies (see Distribution List below) and sponsors, of unanticipated problems.
 - 5.2.3.1 Unanticipated Problem reports will only be sent to OHRP when the event occurred at ECU or an institution that relies on the UMCIRB for review of that particular human research. The UMCIRB will collaborate with that institution to promptly report.
- 5.3 The IRB Chairperson or designee will review all materials when submitted to determine if immediate action is required.
 - 5.3.1 The IRB Chairperson has the authority, upon immediate notification of an unanticipated problem, to suspend enrollment or research procedures to protect participants' safety and welfare; and
 - 5.3.2 The IRB Chairperson's or designee's actions will be reported at the next convened IRB meeting where the unanticipated problem is being reviewed.
- 5.4 The Principal Investigator (PI) and/or study team members will
 - 5.4.1 Promptly determine whether an event needs to be reported to the IRB (and any other appropriate departments/offices/officials) for review. UMCIRB has resources to help make this determination on the UMCIRB website and within the electronic IRB application system.
 - 5.4.1.1 If the event meets the criteria of an Unanticipated Problem, it should be reported within the electronic IRB submission system. Details about the event along with a summary, description of outcomes and corrective action plans are collected within this system.
 - 5.4.1.2 While the UMCIRB would only require reporting if an event met the criteria for an Unanticipated Problem, the investigator should be aware of other applicable reporting requirements to the FDA and/or sponsor per their contractual obligations.
 - 5.4.2 Provide a description of any proposed protocol changes or other corrective actions to be taken by the investigator and/or study team in response to the Unanticipated Problem; and
 - 5.4.3 Contact the UMCIRB for assistance, as needed.

6.0 Procedures:

- 6.1 UMCIRB Staff will:
 - 6.1.1 Assist in review of submitted reports and consult with the UMCIRB Administrative Director (or designee) as needed.
 - 6.1.2 Ensure that any reports that require medical judgment are reviewed by an IRB Chairperson (and IRB member) with sufficient health care training and education.
 - 6.1.3 Ensure the report of Unanticipated Problems are placed on the next available agenda and the minutes accurately reflect the deliberations and determinations of the IRB;
 - 6.1.3.1 The agenda and minutes are available electronically for viewing by

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institutional officials.

- 6.2 If a submitted report implies the potential for immediate harm to participants and others:
 - 6.2.1 UMCIRB staff will notify the UMCIRB Administrative Director or designee, and the appropriate IRB Chairperson or designee;
 - 6.2.2 Collectively the Chair, Director or designee and staff member will make a decision on what action, if any, is required to best protect participants. These actions can include, but are not limited to:
 - 6.2.2.1 suspension of study activities (unless in the best interest of the participant);
 - 6.2.2.2 suspension of participant enrollment; and/or
 - 6.2.2.4 replacing the PI, research staff, or coordinator, to ensure better protection of human participants.
 - 6.2.3 The PI, appropriate institutional officials, sponsor and any relevant regulatory agencies will be immediately notified of the determination by the IRB that is required to protect participants.
- 6.3 The IRB will:
 - 6.3.1 Review unanticipated events involving risks to participants or others which are related or possibly related to participation on the research, are unexpected in nature including the severity or frequency of risks, and suggest the research has the potential for increased risk of harm to the participants or others;
 - 6.3.2 Review the actions taken by the Chairperson or designee regarding suspension of research activities (see Section 6.2.2) and determine whether such actions should be continued, additional actions are required or the imposed actions should be lifted.
 - 6.3.3 Deliberate on any actions required to protect participants' safety and welfare.
 - 6.3.4 Consider whether to suspend any or all research procedures until such time that the risks to participants can be minimized.
 - 6.3.5 Consider whether to terminate the research based on the determination by the IRB that the risks outweigh any potential for benefit from participation, now or in the future.
 - 6.3.6 Provide UMCIRB determinations, in writing, to the Principal Investigator. Actions can include, but are not limited to:
 - 6.3.6.1 Accept the report as submitted, with no further action required
 - 6.3.6.2 Request additional information/clarification.
 - 6.3.6.3 Require the consent document and/or protocol to be revised to reflect information relative to the event.
 - 6.3.5.4 Suspend all or some of the procedures or terminate approval when there appears to be a major risk to participants until such time that the PI can demonstrate that revised procedures have been put in place to protect the welfare and safety of participants.
 - 6.3.5.5 Require additional training for investigators and/or research staff
 - 6.3.7 Verify their agreement of the event being an unanticipated problem that requires reporting.
- 6.4 Distribution List: List of potential agencies or institutional entities which, if providing financial support or have oversight responsibilities, would be notified in the determination of unanticipated problems involving risks to participants or others:

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- 6.1 Agency for International Development (22 CFR 225)
- 6.2 Central Intelligence Agency (Executive order)
- 6.3 Consumer Products Safety Commission (16 CFR 1028)
- 6.4 Department of Agriculture (7 CFR 1c)
- 6.5 Department of Commerce (15 CFR 27)
- 6.6 Department of Defense (32 CFR 219)
- 6.7 Department of Education (34 CFR 97)
- 6.8 Department of Energy (10 CFR 745)
- 6.9 Department of Health and Human Services (45 CFR 46)
- 6.10 Department of Homeland Security (6 U.S.C. section 112)
- 6.11 Department of Housing and Urban Development (24 CFR 60)
- 6.12 Department of Justice (28 CFR 46)
- 6.13 Department of Transportation (49 CFR 11)
- 6.14 Department of Veterans' Affairs (38 CFR 16), Office of Research Oversight
- 6.15 Environmental Protection Agency (40 CFR 26)
- 6.16 National Aeronautics and Space Administration (14 CFR 1230)
- 6.17 National Science Foundation (45 CFR 690)
- 6.18 Social Security Administration (42 U.S.C. section 901)
- 6.19 Food and Drug Administration (21 CFR 56)
- 6.20 Division, Department, or Unit Chairperson and Dean
- 6.21 Administrators at Affiliate site(s)
- 6.22 Any Compliance Officers, Risk Management, or State Agencies that may have a need to be informed
- 6.23 Biomedical and/or Social & Behavioral IRB members and ex-officios

Revision History:

Date	Change	Reference Section(s)
10.01.09	New format; Clarification on authority, procedures, what is reportable	All sections
03.14.14	Updated name of office, font; removed definition of Serious event; clarified PI and/or study team responsibilities	All sections; Definitions section; Responsibilities section
10.09.14	Clarification of responsibilities, reporting and notification procedures and comparison to adverse events	Definitions; Responsibilities; Procedures
01.25.2017	Clarification on sections	Sections 1.0; 3.0; 4.2; 4.5; 6.2; 6.4
5.31.2018	Clarified definition and responsibilities	Sections 4.5, 5.0, 6.4
1.15.2021	Updated office name to UMCIRB from ORIC; added new footer	All sections

References

45 CFR46, Protection of Human Subjects:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.103>

21CFR56, Institutional Review Boards:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=56&showfr=1>

21CFR312, Drugs for Human Use, Investigational New Drug Application:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.32>

OHRP Guidance, January 15, 2007 <http://www.hhs.gov/ohrp/policy/advevntguid.html>