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 an ECU IRB. Federal regulations require research institutions to have a prompt method of notification to 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 nature, severity, or degree of incidence in the investigational plan, protocol, or IRB application (including any supplementary plan or application); includes any adverse experience, 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 IRB application. Some examples could include:
   4.2.1 Any breaches in confidentiality that would place the participant or others at risk.
   4.2.2 Any change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
   4.2.3 Any change to the protocol that was taken without prior IRB approval to eliminate apparent immediate hazard to a research participant; or
   4.2.4 Incarceration of a participant when enrolled on a study not previously
reviewed and approved under the prisoner research provisions. (See SOP: 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: suggests that 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 human subject, 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; and
4.5.2 Only unanticipated events meet one of the criteria for reporting.

5.0 Responsibilities:

5.1 Institutional Review Board will review unanticipated problems involving risks to participants and others that occur on studies approved by the ECU IRB 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 Office of Research Integrity and Compliance (ORIC) Administrative Director or designee will

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 of unanticipated problems to applicable recipients included in the Distribution List (section 6.4), including OHRP;
5.2.3.1 Unanticipated Problem reports will only be sent when the event occurred at an institution that relies on the UMCIRB for review of that particular human research. The ORIC 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 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. ORIC has resources to help make this determination on the ORIC website and within the electronic IRB application system.

5.4.1.1 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 ORIC for assistance, as needed.

6.0 **Procedures:**

6.1 **ORIC Staff will:**

6.1.1 Assist in review of submitted reports and consult with the ORIC 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 institutional officials.

6.2 If a submitted report implies the potential for immediate harm to participants and others:

6.2.1 ORIC staff will notify the ORIC 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 participants).
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 Principal Investigator 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

6.4.1 Agency for International Development (22 CFR 225)
6.4.2 Central Intelligence Agency (Executive order)
6.4.3 Consumer Products Safety Commission (16 CFR 1028)
6.4.4 Department of Agriculture (7 CFR 1c)
6.4.5 Department of Commerce (15 CFR 27)
6.4.6 Department of Defense (32 CFR 219)
6.4.7 Department of Education (34 CFR 97)
6.4.8 Department of Energy (10 CFR 745)
6.4.9 Department of Health and Human Services (45 CFR 46)
6.4.10 Department of Homeland Security (Public law 108-458 Sec. 8306)
6.4.11 Department of Justice (28 CFR 46)
6.4.12 Department of Transportation (49 CFR 11)
6.4.13 Department of Veterans’ Affairs (38 CFR 16), Office of Research Oversight
6.4.14 Environmental Protection Agency (40 CFR 26)
6.4.15 Housing and Urban Development (24 CFR 60)
6.4.16 National Aeronautics and Space Administration (14 CFR 1230)
6.4.17 National Institutes of Health and Human Services (45 CFR 46)
6.4.18 National Science Foundation (45 CFR 690)
6.4.19 Office of Science and Technology Policy (Adoption of policy)
6.4.20 Social Security Administration (Public law 7.5.26)
6.4.21 Food and Drug Administration (21 CFR 56)
6.4.22 DHHS Office for Human Research Protections
6.4.23 External sponsors
6.4.24 Institutional Official
6.4.25 Division, Department, or Unit Chairperson and Dean
6.4.26 Administrators at Affiliate site(s)
6.4.27 Compliance Officers, Risk Management, or State Agencies that may have a need to be informed
6.4.28 Biomedical and/or Social & Behavioral IRB members and ex-officios

Revision History:

<table>
<thead>
<tr>
<th>Date</th>
<th>Revision #</th>
<th>Change</th>
<th>Reference Section(s)</th>
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<tbody>
<tr>
<td>10.01.09</td>
<td>1.1</td>
<td>New format; Clarification on authority, procedures, what is reportable</td>
<td>All Sections</td>
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<tr>
<td>03.14.14</td>
<td>1.2</td>
<td>Updated name of office, font; removed definition of Serious event; clarified PI and/or study team responsibilities</td>
<td>All sections; Definitions section; Responsibilities section</td>
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<tr>
<td>10.09.14</td>
<td>2.0</td>
<td>Clarification of responsibilities, reporting and notification procedures and comparison to adverse events.</td>
<td>Definitions; Responsibilities; Procedures</td>
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<td>3.0</td>
<td>Clarification on sections</td>
<td>Sections 1.0; 3.0; 4.2; 4.5; 6.2; 6.4</td>
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References

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.103
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfsearch.cfm?cfrpart=56&showfr=1