Unanticipated problems are problems that arise during the conduct of the research that may involve risks to subjects or others that are:

1. Unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB) approved research protocol and informed consent document and the characteristics of the subject population being studied; and

2. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, social, legal, or economic) than was previously known or recognized.

Researchers must promptly report all unanticipated problems that may involve risk to subjects or others to the Michigan State University (MSU) IRB. Any unanticipated problem that may involve risk to subjects or others that also constitutes an adverse event shall be reported, and will be reviewed, following these policies and procedures. The IRB chair, in consultation as appropriate with the others (e.g. IRB, Human Research Protection Program (HRPP) director), determines whether the reported unanticipated problem did involve risks to subjects or others, whether the investigator satisfactorily resolved the problem, and whether corrective/protective actions are required. Unanticipated problems determined to involve risk to subjects and others shall be reported to appropriate officials and government agencies pursuant to HRPP Manual 4-8 “Reporting Policy.”

This policy and procedures reflects the U.S. Office for Human Research Protection’s (OHRP) current guidance on unanticipated problems involving risk to subjects or others and adverse events. Only a small subset of adverse events occurring in human subjects participating in research will meet the definition of an unanticipated problem involving risk to subjects or others. Internal and external adverse events should only be reported to the IRB if the adverse event is determined to meet the criteria for an unanticipated problem that may involve risks to subjects or others. The principal investigator (PI) should assess whether it meets the definition of an unanticipated problem involving risks to subjects or others (see “Adverse Event Assessment” below). If an adverse
event is submitted to the IRB, it must include a clear explanation of why the adverse event has been determined to be an unanticipated problem and a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

However, if the U.S. Food and Drug Administration (FDA) Humanitarian Use Device (HUD) regulation (21 CFR 814) applies to the activity, "the medical device reports submitted to FDA in compliance with the requirements of part 803 of this chapter shall also be submitted to the IRB of record." 21 CFR 814.126(a).

**Initial Reporting to the IRB**
Investigators must report all unanticipated problems that may involve risk to subjects or others to the IRB within the specified time frame.

**Reportable Events**
Reportable events include:
- Breach of confidentiality (e.g., lost or stolen research data)
- Newly discovered information (e.g., from data analysis or publications) that indicates a greater risk to subjects than expected and that may affect adversely the safety of the subjects or the conduct of the clinical trial
- Changes made to research without prior IRB approval in order to eliminate apparent immediate harm
- Incorrect dosing or labeling that adversely affects the safety of subjects
- Risk to others (e.g., research staff, investigators) related to the research (e.g., physical harm)
- Adverse events which meet the definition of an unanticipated problems involving risks to subjects or others (unexpected, involve new or increased risk, and are related to the research)
- Unexpected serious adverse event
- Unanticipated adverse device effect
- Unsafe research environments
- Threats to subjects or others related to their participation in the research
- Changes in the research environment that increase the risk to subjects or others due to the research (e.g., political or social changes)
- Higher occurrence of an adverse event or serious adverse event than expected
- Any side effect not mentioned in the consent form or protocol
- Incarceration of subjects

**Reporting Time Frame**
For urgent unanticipated problems (problems that pose immediate harm to subjects or others), investigators may implement a change in protocol prior to IRB approval to eliminate a hazard to subjects or others. See HRPP Manual 9-5 “Unapproved Change in Protocol” for policies and procedures. Investigators should contact the IRB for guidance when needed.
If the unanticipated problem resulted in a subject death, was potentially life threatening, or risked serious harm to the subject, the investigator should report the problem to the MSU IRB within 24 hours of knowledge of the event or sooner as appropriate. For adverse events that may constitute an unanticipated problem, the investigator should complete and submit the clinical unanticipated problem reporting form with any pertinent supporting documents (e.g., study sponsor report, communications) within 72 hours to the IRB. For all other unanticipated problems, the non-clinical unanticipated problem reporting form with any pertinent supporting documents (e.g., study sponsor report, communications) should be completed and submitted by the investigator within 72 hours to the IRB.

Investigators should not delay reporting for lack of complete information; follow-up information may be submitted.

If an unanticipated problem occurs at a CRIRB performance site, the PI should report within the required time frame to both the chair of the local IRB and the chair of the CRIRB.

Immediate Actions
The IRB chair determines if immediate actions are necessary. The IRB chair will review the report (e.g., completed form, supporting documents such as study sponsor report) and any other pertinent documents submitted by the investigator upon receipt and/or make an inquiry into the situation.

Immediate issues to consider will be:
- Protect subjects by suspending the protocols according to HRPP Manual 9-3 “Termination or Suspension of Research”
- Notify officials who will take appropriate action (e.g., notify Contract and Grant Administration)

The IRB chair may reach this decision with consultation from other members of the IRB. At any time during the review of a reported unanticipated problem that may involve risk to subjects or others, the IRB chair or IRB may determine that it is necessary to act to protect human subjects by suspending the protocols according to HRPP Manual 9-3 “Termination or Suspension of Research.”

Clearly Not an Unanticipated Problem Involving Risks to Subjects or Others
Reported unanticipated problems that clearly do not meet the definition of unanticipated problems involving risks to subjects or others (e.g., postage for survey was more expensive than anticipated) should be documented in the IRB file by the IRB chair.

Investigation
Incidents that may constitute unanticipated problems involving risks to subjects or others are investigated by the IRB chair. Materials reviewed by the IRB chair include the verbal report (if applicable), the written report submitted by the investigator (e.g., unanticipated problems (clinical or non-clinical) reporting form, any supporting
documents, study sponsor report, communications) and the IRB file. The IRB chair will work with the investigator to gather more information, if needed.

The IRB chair may determine that additional review by IRB member(s) is needed. If the IRB chair determines that such review is necessary, the IRB member(s) will receive the verbal report (if applicable), the written report submitted by the investigator (e.g., unanticipated problems (clinical or non-clinical) reporting form, any supporting documents, study sponsor report, communications) any pertinent communications between the IRB staff and the investigator, and the IRB file (if necessary). If any IRB member feels that he/she is not qualified to review the research study, the IRB staff should be notified. The IRB chair will be consulted to determine an appropriate replacement. If an appropriate replacement is not available, HRPP Manual 5-4 “Additional Expertise” policy and procedures will be followed.

**Convened IRB Review**

The IRB chair presents the potential unanticipated problem involving risk to subjects or others to the convened IRB for review. Materials provided to IRB members include the verbal report, the written report submitted by the investigator (e.g., unanticipated problems (clinical or non-clinical) reporting form, any supporting documents, study sponsor report, communications), any pertinent communications between the IRB staff and the investigator, and copies of the pertinent sections of the IRB file. The complete IRB file will be available for review (if necessary).

**Further Investigation**

The IRB may require further investigation prior to making a determination of whether the event constituted an unanticipated problem involving risks to subjects or others. If further investigation is required, the IRB may:

- Request the IRB chair continue his/her investigation
- Impanel an investigative sub-committee of the IRB to review all relevant materials, i.e., the verbal report (if applicable), the written report submitted by the investigator (e.g., unanticipated problems (clinical or non-clinical) reporting form, any supporting documents, study sponsor report, communications), any pertinent communications between the IRB staff and the investigator, and the IRB file (if necessary)
- Obtain additional expertise (See HRPP Manual 5-4 “Additional Expertise”)

The IRB chair, investigative sub-committee, or additional expert will report back to the convened IRB with recommendations. The IRB will then make the determination of whether the unanticipated problem involved risk to subjects or others.

**IRB Determinations**

The IRB determines whether the unanticipated problem involved risks to subjects or others. This decision is based on the definition of an unanticipated problem involving risks to subjects or others. When the IRB is reviewing adverse events to determine whether they constitute an unanticipated problem involving risk to subjects or others, the IRB should also see the Adverse Event Assessment section below.
The IRB will determine whether the investigator satisfactorily resolved the problem, if applicable, and whether corrective/protective actions are necessary. Corrective/protective actions which may be taken include, but are not limited to:

- Require research study specific corrective action
- Require a plan for corrective action, based on the type and nature of the issues
- Require education of the researchers
- Modification of the protocol
- Modification of inclusion or exclusion criteria (e.g., to mitigate newly identified risks)
- Modification of informed consent process and/or documents (e.g., include description of newly recognized risks, information disclosed during consent process)
- Require observation or monitoring of the consent process (e.g. IRB staff, member, chair, human research liaison)
- Require that subjects be re-contacted and provided with updated information or consent
- Require current subjects to re-consent to participation
- Provide additional information to past subjects
- Notification of current subjects when such information may relate to the subjects’ willingness to continue to take part in the research
- Suspension of enrollment of new subjects
- Suspension of research procedures in currently enrolled subjects
- Suspension of the research
- Termination of the research
- Modification of the continuing review schedule
- Additional procedures for monitoring (e.g., subjects, consent process, research) or routine audits
- Referral to other organizational entities
- Other actions as needed
- No action may be needed

Required actions will be communicated to the PI in writing.

**Reporting**

Unanticipated problems that involve risk to subjects and others will be reported (e.g., to institutional officials, government agencies) pursuant to policies and procedures in HRPP Manual 4-8 “Reporting Policy.”

**Noncompliance**

Unanticipated problems that also constitute noncompliance with federal regulations and university policies and procedures are subject to policies and procedures in HRPP Manual 9-2 “Noncompliance.”
Adverse Event Definitions
The definitions found below are modified from “Guideline for Industry Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A.”

Adverse event: Any untoward or unfavorable medical occurrence in a clinical investigation with a human subject administered a pharmaceutical product or medical device and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g., abnormal laboratory finding, physical exam), system or disease temporally associated with the use of a medicinal product or device, whether or not considered related to the medicinal product or device.

External adverse event: An adverse event experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. External adverse events occur in the context of multi-center clinical trials.

Internal adverse event: An adverse event experienced by subjects enrolled by the investigator(s) or study team subject to oversight by an MSU IRB. For single-center clinical trials, all adverse events would be considered internal adverse events.

Local subject: A subject that has been enrolled by the MSU researchers for the MSU approved research study.

Non-local subject: A subject that has not been enrolled by the MSU researchers for the MSU approved research study (i.e., for multi-site, clinical studies).

Serious adverse event: Any untoward medical occurrence that at any time:
- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based on 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

Unanticipated adverse device effect: “Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.” 21 CFR 812.3(s)

Unexpected adverse event or unexpected serious adverse event: An adverse event or serious adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., investigator’s brochure, protocol or informed consent).
**Adverse Event Assessment**

1. Whether the unexpected adverse event is an adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency 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:
      i. Protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and
      ii. Other relevant sources of information, such as product labeling and package inserts; or
   b. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposition risk factor profile for the adverse event.

2. Whether the adverse event is related or possibly related (there is a reasonable possibility that the adverse event may have been caused by the procedures) to participation in research:
   a. Considered related to the research if at least partially caused by:
      i. The procedures in the research.
   b. Considered unrelated to the research if the adverse event solely caused by:
      i. Underlying disease, disorder, or condition of the subject.
      ii. Other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

3. Whether an adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.
   a. Whether the adverse event is considered a serious adverse event (see Definitions).