

Michigan State University Human Research Protection Program	
<i>Subject: Unanticipated Problems</i>	
<i>Section: 9-1</i>	<i>This policy and procedure supersedes those previously drafted.</i>
<i>Reviewed by: IRB, URC, UGC, MSU Legal Counsel; Revision reviewed by HRP/IRB Administrative Committee.</i>	<i>Approved by: Vice President of Research and Graduate Studies, 4-21-2005; Revision approved by the Vice President of Research and Graduate Studies on 2-1-2006.</i>
<i>Related Sections: 4-8, 5-4, 9-2, 9-3</i>	

Policy

Investigators must report all unanticipated problems that may involve risk to subjects or others to the MSU IRB. Any unanticipated problem that also constitutes an adverse event should be reported, and will be reviewed, following these policies and procedures. The IRB chair, in consultation with the IRB, determines whether the reported unanticipated problem involved 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 will be reported to appropriate officials and government agencies pursuant to Section 4-8, "Reporting Policy" of the HRP Manual.

Procedures

1. Investigators must report all unanticipated problems that may involve risk to subjects or others to the IRB within the specified time frame.
 - a. Reportable events
 - i. Breach of confidentiality (e.g., lost or stolen research data)
 - ii. Newly discovered information (e.g., from data analysis or publications) that indicates a greater risk to subjects than expected
 - iii. Change in protocol implemented prior to IRB approval to eliminate a hazard to subjects or others
 - iv. Incorrect dosing or labeling
 - v. Risk to others (e.g., research staff, investigators) related to the research (e.g., physical harm)
 - vi. Unexpected AE or SAE
 - vii. Unanticipated adverse device effect
 - viii. Unsafe research environments
 - ix. Threats to subjects or others related to their participation in the research
 - x. Changes in the research environment that increase the risk to subjects or others due to the research (e.g., political or social changes)
 - xi. Higher occurrence of an AE or SAE than expected
 - xii. Any side effect not mentioned in the consent form or protocol
 - xiii. Incarceration of subjects
 - b. Reporting time frame

- i. For urgent unanticipated problems (problems that pose immediate harm to subjects or others), the investigators may implement a change in protocol prior to IRB approval to eliminate a hazard to subjects or others. See Section 9-5, "Unapproved Change in Protocol" of the HRP Manual for policies and procedures. Investigators should contact the IRB for guidance when needed.
 - ii. *Initial Verbal Report.* The investigator should verbally report all unanticipated problems (including clinical unanticipated problems) to the MSU IRB within 24 hours of knowledge of the event.
 - iii. *Written Report.*
 1. For clinical unanticipated problems, the investigator should complete and submit the Local Patient Adverse Event/Clinical Unanticipated Problem form with any pertinent attachments (e.g., study sponsor report, communications, etc) within 2-3 days to the IRB.
 2. For all other unanticipated problems, the Unanticipated Problem form with any pertinent attachments (e.g., study sponsor report, communications, etc) should be completed and submitted by the investigator within 2-3 days to the IRB.
 - iv. If an unanticipated problem occurs at a CRIRB performance site, the responsible project investigator should report within the required time frame to both the chair of the local Institutional Review Board (IRB) and the chair of the CRIRB.
 2. The IRB chair determines if immediate actions are necessary.
 - a. The IRB chair will review the verbal (if applicable) and/or written report (e.g., completed form, attachments such as study sponsor report, etc.) and any pertinent attachments submitted by the investigator upon receipt and/or make an inquiry into the situation.
 - b. Immediate issues to consider will be:
 - i. Protect subjects by suspending the protocols according to Section 9-3, "Termination or Suspension of Research" of the HRP Manual
 - ii. Notify officials who will take appropriate action (e.g., notify Contract and Grant Administration)
 - c. The IRB Chair may reach this decision with consultation from other members of the IRB.
 - d. 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 Section 9-3, "Termination or Suspension of Research" of the HRP Manual.
 3. The IRB chair investigates the report.
 - a. Materials reviewed by the IRB chair include the verbal report (if applicable), the written report submitted by the investigator (e.g., Unanticipated Problem form or Local Patient Adverse Event/Clinical Unanticipated Problem form, any

- attachments, study sponsor report, communications, etc.) and the IRB project file.
- i. The IRB chair will work with the investigator to gather more information, if needed.
 - ii. The IRB chair may determine that additional review by IRB member(s) is needed.
 1. 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 Problem form or Local Patient Adverse Event/Clinical Unanticipated Problem form, any attachments, study sponsor report, communications, etc.) any pertinent communications between the IRB staff and the investigator and the IRB file (if necessary).
 2. If any IRB member feels that he/she is not qualified to review the project, the IRB staff should be notified. The IRB chair will be consulted to determine an appropriate replacement.
 3. If an appropriate replacement is not available, the Additional Expertise policy and procedures will be followed, Section 5-4.
4. The IRB Chair, alone or in consultation with the IRB, determines whether the unanticipated problem involved risks to subjects. This decision is based on:
 - a. relation of problem to research
 - b. the risk posed to subjects or others
 5. All unanticipated problems determined to involve risks to subjects or others will be brought to the IRB for discussion or as an informational item.
 6. At the IRB chair's discretion, unanticipated problems determined not to involve risk to subjects or others may be brought to the IRB for discussion or as an informational item.
 7. The IRB chair determines:
 - a. whether the unanticipated problem should be brought to the IRB for information or discussion
 - b. whether IRB consultation is needed to determine:
 - i. whether the investigator satisfactorily resolved the problem, if applicable
 - ii. whether corrective/protective actions are necessary,
 1. actions which may be taken include:
 - a. Require project specific corrective action.
 - b. Require a plan for corrective action, based on the type and nature of the issues.
 - c. Require education of the investigators and research team.

- d. Require that subjects be re-contacted and provided with updated information or consent.
 - e. Suspend or terminate the study.
 - f. More frequent intervals of continuing review.
 - g. Monitoring/routine audits
 - h. Other actions as needed.
 - i. No action may be needed.
2. required actions will be communicated to the responsible project investigator in writing
8. If an unanticipated problem is brought to the IRB for consultation or discussion, the following materials (if applicable) provided to IRB members include:
- a. the verbal report
 - b. the written report submitted by the investigator (e.g., Unanticipated Problem form or Local Patient Adverse Event/Clinical Unanticipated Problem form, any attachments, study sponsor report, communications, etc.)
 - c. any pertinent communications between the IRB staff and the investigator
 - d. copies of the pertinent sections of the IRB file
 - e. the complete IRB file will be available for review (if necessary)
9. 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 Section 4-8, "Reporting Policy" of the HRP Manual.
10. Unanticipated problems that also constitute noncompliance with federal regulations and university policies and procedures are subject to policies and procedures in Section 9-2, "Noncompliance" of the HRP Manual.

Definitions

Unanticipated problems are problems that arise during the conduct of the research that may involve risks to subjects or others that are not mentioned in the study protocol or informed consent. Risks can be defined as the probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study.

Clinical unanticipated problems include unexpected adverse events and unexpected serious adverse events. The definitions found below are modified from "Guideline for Industry Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A".

An ***adverse event (AE)*** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or medical device and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), 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.

A **serious adverse event (SAE)** is any untoward medical occurrence that at any time does result in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

An **unexpected AE** or **unexpected SAE** is an AE or SAE, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure, protocol or informed consent).

“Unanticipated adverse device effect means 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)

Local subject is a subject that has been enrolled by your study team.

Non-local subject is a subject that has not been enrolled by your study (i.e., for multi-site, clinical studies)