

ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**Part 1****Policy No. XXIII.****Subject: Unanticipated Problems Involving Risks to Subjects or Others****Purpose**

The purpose of this policy is to ensure events that may represent unanticipated problems involving risks to subjects and others including unexpected and related adverse events are promptly reported to the Main Line Hospitals Institutional Review Board (MLH IRB) in accordance with regulatory requirements of the Department of Health and Human Services (DHHS) (45 CFR 46.103 (b) (5)) and the Food and Drug Administration (FDA) (21 CFR 56.108(b) (1)).

Definitions**1. Unanticipated Problems**

Unanticipated problems involving risks to subjects or others are defined as any incident, experience or outcome that meets all of the following criteria:

- a) Unexpected (in terms of nature, severity, or frequency) given the research procedures and the subject population being studied; **and**
- b) Related or possibly related to a subject's participation in the research; **and**
- c) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

NOTE: "Possibly related" means that there is a reasonable possibility that the event may have been caused by the procedures/drugs/devices involved in the research.

2. Adverse event

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

3. Serious Adverse Event (SAE)

Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- A life-threatening event (places the subject at immediate risk of death from the event as it occurred);

- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly or 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 outcomes in this definition

4. Unanticipated Adverse Device Effect (UADE):

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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Reportable Problems/Events

An adverse event (or serious adverse event) may be expected, based on the known risks of the study and information in the informed consent and other study related documents. An adverse event is reportable only if it is also an unanticipated problem. In addition, unanticipated problems, even if not involving physical risks, need to be reported.

Prompt reporting of the following unanticipated problems or events is required;

1. Event (including adverse event reports, injuries, side effects, breaches of confidentiality, or other problems occurring to subjects enrolled at this site or other sites in the same study) that occurs any time during or after the research study, which in the opinion of the principal investigator:

- Involved harm to one or more subjects or others, or placed one or more subjects or other at increased risk of harm; **and**
- Is unexpected (an event is unexpected when it is not described with specificity in the protocol, informed consent and other study related documents; or if described with specificity, it occurs beyond the expected frequency and/or severity; **and**
- Is related to the research procedures (an event is related to the research procedures if in the opinion of the principal investigator it was at least possibly caused by the research procedures.)

2. Information that indicates a change in the risk/benefit ratio of the research. For example:

- An interim analysis indicates that subjects have a lower rate of response to treatment than initially expected
- Safety monitoring indicates a particular side effect is more severe, or more frequent than initially expected
- A paper is published from another study and shows an arm of the research study is of no therapeutic value

3. A single occurrence of a serious adverse event that is unexpected and that is commonly and strongly associated with drug exposure (such as angioderma, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)

4. A single occurrence, or more often a small number of occurrences of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
5. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
6. Change to the protocol without prior IRB review necessary to eliminate an apparent immediate hazard to research subject(s)
7. Incarceration of a subject in a protocol not approved to enroll prisoners and the investigator considers it in the subject's best interest to remain in the study
8. An event for which the protocol requires prompt reporting to the sponsor
9. Complaint of a subject when the complaint indicates unexpected risks or the complaint can not be resolved by the research team
10. Protocol violation (an accidental or unintentional change to the IRB approved protocol) that placed one or more subjects at risk, or has the potential to occur again.
11. An unanticipated adverse device effect. Any serious adverse effect on the health or safety, or any life-threatening problem associated with an investigational device.

Procedures

The PI reports problems under this policy by completing and submitting the MLH IRB Form 004 to the Office of Research Affairs. The report should be submitted as soon as possible after the PI learns of the event but in all cases within 10 working days.

NOTE: When a death is unforeseen and indicates subjects or others are at an increased risk of harm, the PI is required to report the death within 24 hours of knowledge of the event.

The Office of Research Affairs will review the submission to determine if it meets the definition of an unanticipated problem involving risks to subjects or others.

In the rare instance that the ORA Director (or Institutional Official in the absence of the ORA Director) and IRB Chairman (or vice-chairman in the absence of the Chairman) jointly determine that an immediate and life-threatening hazard exists for all subjects enrolling in the study, the Chairman (or vice-chairman) shall suspend the study immediately until the matter can be considered by a convened IRB subcommittee in accordance with SOP XXIV.

The convened board will review events that meet the criteria for an unanticipated problem as defined in this policy. All members of the convened IRB receive the report form, the currently approved consent form and any supplemental information deemed relevant by the ORA and the IRB chair to conduct a thorough review. Based on the nature of the event and the expertise required to assess it the IRB chair or designee acts as the primary reviewer and presents his findings to the convened IRB.

The convened IRB will consider the following actions during its deliberations:

- Accept the report with no additional requirements
- Approve the investigator's proposed changes
- Place the study on administrative hold pending IRB receipt of further information from the PI in a time period not to exceed 60 days
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to past subjects
- Providing additional information to current subjects (This must be done whenever the information relates to the subject's willingness to continue participation)
- Requiring current subjects to re-consent
- Alteration of the frequency of continuing review
- Monitoring of the research and/or consent process
- Requiring additional training of the investigator and/or research team
- Suspension or termination of the research
- Referral to other organizational entities for further investigation

If the IRB determines that the event was an unanticipated problem involving risks to subjects or others, the matter is handled according to SOP XXIV under reporting procedures.

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