

St. John Hospital and Medical Center Institutional Review Board (IRB)

POLICY: Continuing Review – Ongoing Review

This portion of the SJH&MC IRB Standard Operating Procedures Policy on “Continuing Review – Ongoing Review” has been revised and approved for immediate implementation by the IRB on 6/18/09. This version supersedes all previous versions.

1.2 Serious and Unexpected Adverse Events

Subject safety is of the greatest importance for both the individual subject and the goals of the clinical study. The purpose of continuing review and monitoring of an on-going study is to ensure that the research remains justified and that the rights and welfare of the participants continue to be fully protected. Accordingly, if a local research subject sustains any unanticipated problem that causes risk or harm to the subject that is related or possibly related, to the research intervention this constitutes a reportable event. If the event is serious and unexpected, prompt reporting to the Sponsor and to the IRB is mandatory.

Definitions of Unanticipated Reportable Problem:

- (1) **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- (2) **Related** or **possibly related** to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involving in the research); and
- (3) **Serious** 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; and may include, but not limited to:
 - 1) results in death, or
 - 2) is life-threatening, or
 - 3) requires inpatient hospitalization or prolongation of existing hospitalization, or
 - 4) results in persistent or significant disability or incapacity, or
 - 5) results in a congenital anomaly or birth defect, or
 - 6) causes cancer, or
 - 7) is an overdose, or
 - 8) is any medical event which requires treatment to prevent one of the medical outcomes listed above.

If the internal event is serious, related or possibly related, and unexpected, prompt reporting to the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) and to the IRB is mandatory.

Definition of Reportable Adverse Event:

The term adverse event is not defined in the regulations, nor is there a widely accepted definition in the regulatory community. However, OHRP adopted a working definition in its January 15, 2007 Guidance, which states:

An **adverse event** is defined as:

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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

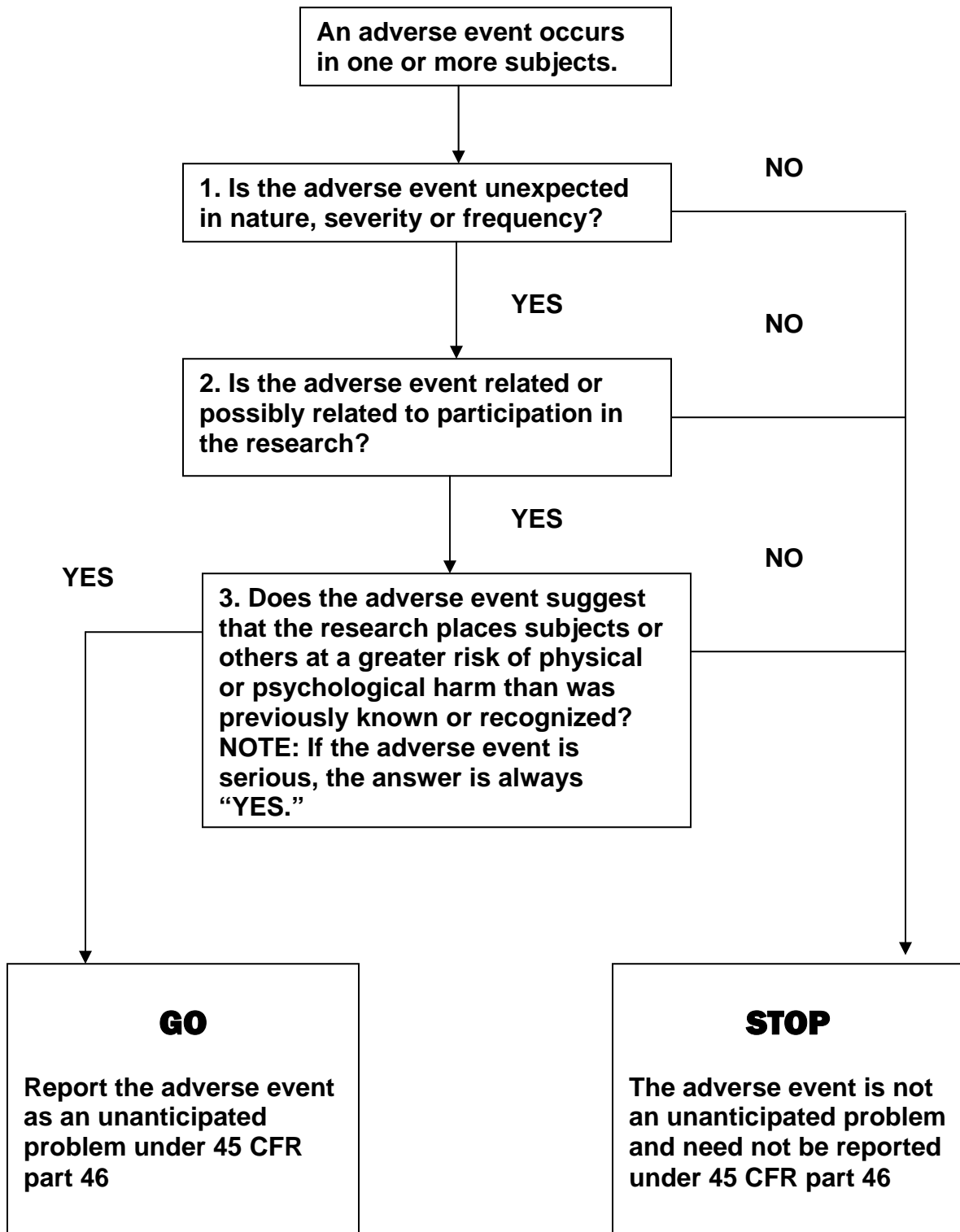
Adverse events encompass both physical and psychological harms. They occur most frequently in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

In the context of Multicenter clinical trials, adverse events can be characterized as either *internal adverse events* or *external adverse events*. From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution, whereas *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

In the case of an *internal adverse event* at a particular institution, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution, or the subject's healthcare provider. In the case of *external adverse events*, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external adverse events represent the majority of adverse event reports currently being submitted by investigators to IRBs.

OHRP has provided the following algorithm for determining whether an adverse event is an unanticipated problem:

**Algorithm for Determining Whether an Adverse Event
is an Unanticipated Problem**



1.2.1. Internal Reportable Problem.

To determine if an adverse event is an unanticipated reportable problem, the investigator should answer the following questions:

- 1) Is the adverse event unexpected?
- 2) Is the adverse event related or possibly related to participation in the research?
- 3) Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is yes, then the adverse event is an unanticipated problem and prompt reporting to the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) and the IRB are mandatory. The investigator should also report events that in the judgment of the investigator alter or potentially alter the risk to participants in the study.

The investigator must complete and submit an IRB Report of Unanticipated Internal Problem or Adverse Event to the IRB within 48 hours, but no later than five (5) days, of the reportable event. The IRB will expect the investigator to also provide them with a determination of whether or not the investigator finds modifications to the informed consent form are necessary as a result of these adverse event reports.

The internal unanticipated problems and/or adverse event reports will be reviewed by the IRB Chairperson or designee. If the Chairperson determines that action may be needed to protect the safety of research subjects due to the nature or frequency of reported adverse events, he/she may take such action and/or the full IRB or designated subcommittee will review the adverse events and study in question to determine action, if any, by the IRB. The IRB, or designated subcommittee, will review summaries of all unanticipated problems and serious adverse events as soon as possible at a convened meeting.

1.2.2. External Adverse Events (Multicenter clinical trials)

Reports of individual external (or events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial, or “non-local”) adverse events often lack sufficient information to allow investigators or IRBs engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or other at a greater risk of physical or psychological harm than was previously known or recognized.

Under current OHRP and FDA guidance, it is neither useful nor necessary for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB per the federal regulations.

Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the

research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

To that end, the IRB will expect investigators to only submit, upon receipt, the DSMB/DMC or other study monitoring entity's report when a particular external adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem. Additionally, the IRB will expect sponsors to provide local investigators with periodic summary reports or aggregated adverse event information in place of individual safety reports to be submitted to the local IRB.

The DSMB/DMC or other monitoring entity reports submitted to the IRB by investigators should include:

- 1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem;
- 2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem; and
- 3) a recommendation for or against changes to the informed consent form.

When an investigator receives a report of an external adverse event, before submitting the report to the IRB, the investigator should review the report and assess whether it identifies the adverse event as being:

- 1) unexpected;
- 2) related or possibly related to participation in the research; and
- 3) serious or otherwise suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only external adverse events that are identified in the DSMB/DMC or other monitoring entity report(s) as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems.

If an external adverse event(s) is not an unanticipated problem (as clearly defined above), the report(s) will no longer be reviewed by the IRB.

1.3 Reporting Requirements for Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOs):

All unanticipated problems involving risks to subjects or others must be reported promptly to the IRB. A UPIRSO is defined as any unforeseen event or events that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research.

They are problems that arise during research that may involve risks to subjects or others that are:

1. *Unexpected* (e.g. nature, severity or frequency) given:
 - A. Research procedures that are described in protocol-related documents; &
 - B. Characteristics of subject population being studied;
2. Related or possibly related to participation in the research (e.g., *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggest *research places subjects* or other at *greater risk of harm* (e.g., physical, psychological, social, legal, economic) than was previously known / recognized.

UPIRSOs can occur in all kinds of research, not just medical studies. For example, a stolen laptop with research data can be a UPIRSO. Other examples might include, but are not limited to: difficulty recruiting subjects, higher than expected adverse events, higher than expected subject drop out rate, higher than expected protocol deviation rate, loss of multiple staff members, injury to a staff member while conducting study-related procedures, or subject difficulty understanding the informed consent.

If a UPIRSO occurs, **prompt reporting to the IRB is required** (see timelines below):

Urgent unanticipated problems (problems that pose immediate harm to subjects or others):

- Change may be implemented in protocol prior to IRB approval to eliminate a hazard to subjects or others. Contact the IRB for guidance when needed.

Unanticipated problem resulted in subject death, was potentially life threatening or risked serious harm to subject:

- Within 24 hours of knowledge of event or sooner as appropriate.

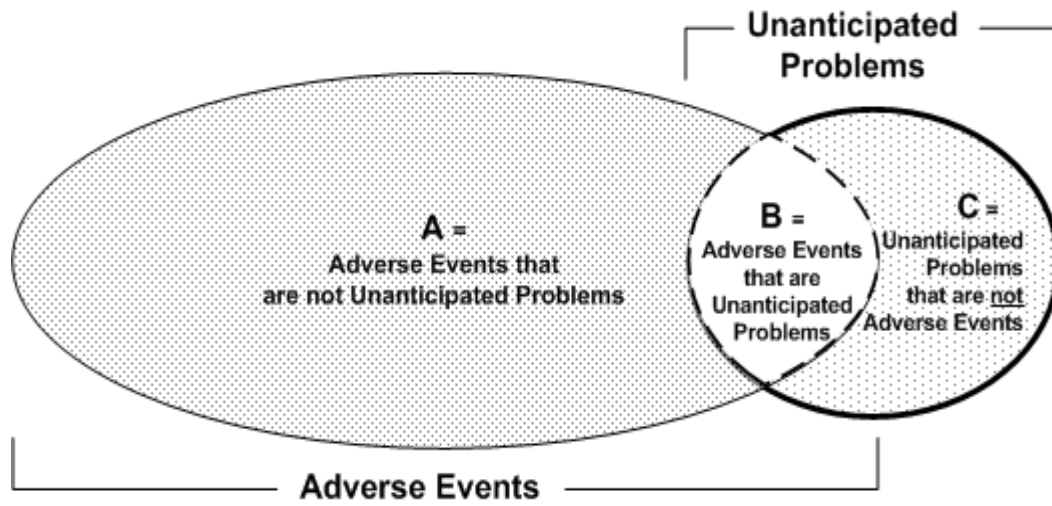
For adverse events that may constitute an unanticipated problem:

- Within 72 hours
- Complete & submit Clinical Unanticipated Problem form with any pertinent attachments (e.g., study sponsor report, communications, etc.)

For all other unanticipated problems:

- Within 72 hours
- Complete & submit Non-Clinical Unanticipated Problem form with any pertinent attachments (e.g., study sponsor report, communications, etc.)

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



Under 45 CFR part 46: Do not report A, Do report (B+C)

<http://hhh.gov/ohrp/policy/AdvEvtGuid.htm>