

Hebrew SeniorLife Institutional Review Board Adverse Event Reporting Guidelines

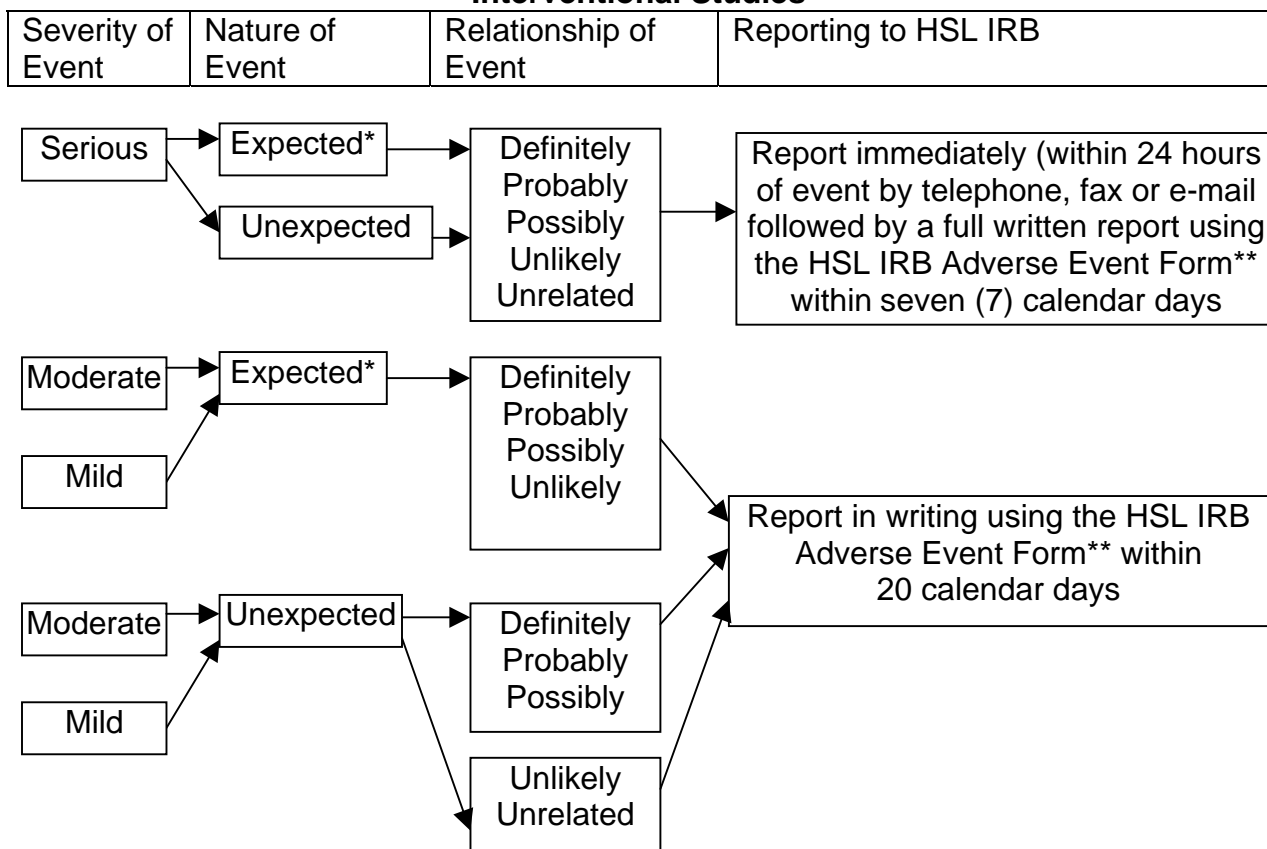
Adverse event reporting and review: Serious adverse events should be reported to the IRB within 24 hours of occurrence via fax or e-mail with a written report submitted within seven (7) calendar days. The IRB will review adverse events that are serious in nature at the next convened meeting – unless otherwise specified or recommended by the IRB Chair.

The PI must submit any reports regarding the event to the IRB, once available. If reports are not available when the IRB first reviews the event, the Chair will review the report and determine if it should be reviewed by the IRB, or if the report does not warrant further review and can be filed with the other study documents. The IRB staff will ensure that the entire study file is on-hand at the meeting for review, if necessary.

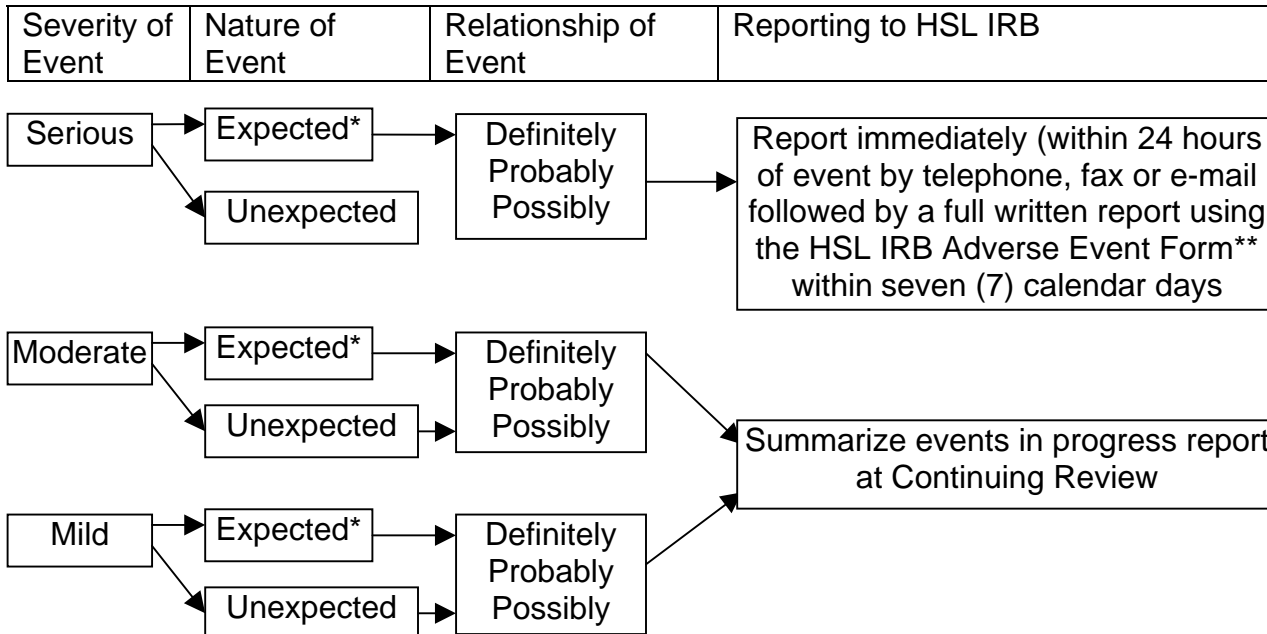
For **interventional** studies, the principal investigator must complete appropriate adverse event form and forward to the IRB of record for the protocol within the required time frame for reporting, but in no case beyond these time frames. Investigators are encouraged to report events as soon as possible within the required time frame. Refer to Flowchart below for reporting requirements for **interventional** studies.

For **non-interventional or observational** studies, i.e., studies that do not involve an intervention or alteration in standard clinical care, adverse events that are not serious need **not** be reported because the events will not be related to the study itself. **If, however, subject complaints arise from an observational study, the IRB should be notified in writing of the subject's concern and how the concern was addressed.** Refer to Flowchart below for reporting requirements for **non-interventional or observational** studies.

Interventional Studies



Non-interventional or Observational Studies



- (1) Report all serious adverse events that occur after active study participation for a minimum of 30 days post study discontinuation or as specified in the protocol, whichever time period is greater if the event is thought to be possibly, probably, or definitely related to the study drug/biologic, device or other study-related intervention or diagnostic procedure.
- (2) *Reporting of expected serious adverse events to the IRB is not required prior to continuing review for NIH-sponsored cooperative Group trials, such as NCI sponsored oncology trials or certain AIDS trials. Refer to the sponsor's protocol for specific reporting requirements.
- (3) ** A study specific Adverse Event form that is approved for use by HSL IRB and Data Safety Monitoring Board may be substituted.

The following terms are defined as they are being used in this policy and for the reporting guidelines.

Interventional Studies: Interventional studies include research designed to evaluate the safety, effectiveness, or usefulness of therapies (e.g., drugs, diet, exercise, surgical interventions, or medical devices), diagnostic procedures (e.g., CAT scans or prenatal diagnosis through amniocentesis, chorionic villi testing, and fetoscopy, or preventive measures (e.g., vaccines, diet, or fluoridated toothpaste).

Non-interventional Studies: Studies on normal human functioning and development that involve limited invasive or non-invasive procedures, e.g., blood or urine collection, moderate exercise, fasting, feeding, sleep, learning, responses to mild sensory stimulation, surveys or questionnaires, etc. are, for the purposes of this policy, considered non-interventional studies.

Observational Studies: Observational studies include research that does **not** involve any intervention, alteration in standard clinical care or use in subjects of any invasive or non-invasive procedure. Studies limited to the recording of data on individuals receiving standard medical care, the use of existing specimens or data, or the retrospective review of health information are, for the purposes of this policy, considered observational studies.

Adverse Event: Any untoward medical occurrence that may present itself during the conduct of a research study and which may or may not have a causal relationship with the study procedures.

IND Safety Reports: Sponsor generated reports of serious and unexpected adverse events occurring at any participating site that are distributed to all other participating sites.

Data Safety Monitoring Board (DSMB): DSMB's review data on such aspects as participant enrollment, site visits, study procedures, forms completion, data quality, losses to follow-up and other measures of adherence to the protocol, including reports of toxicity. The Board makes recommendations based on those data, regarding appropriate protocol and operational changes.

IND SAFETY REPORTS AND DATA SAFETY MONITORING BOARD REPORTS (DSMB)

The principal investigator must review Sponsor IND Safety Reports and DSMB reports and forward them to the IRB of Record within seven (7) calendar days of receipt of report.

Serious adverse events (21 CFR 312.32) are events that result in any of the following outcomes: death; a life threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. In addition, events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may

jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Mild adverse events: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.

Moderate adverse events: Discomfort severe enough to cause interference with usual activities; persistent or requiring treatment.

Unexpected adverse events (21 CFR 312.32) are defined as any event, 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 investigative plan or elsewhere in the current application, as amended. "Unexpected", as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.

Expected adverse events are defined as any event, the specificity or severity of which is consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is consistent with the risk information described in the general investigative plan or elsewhere in the current application, as amended.

Policy Statement

Adverse event reporting to the IRB and, in some circumstances, Federal agencies, is required by Federal regulation. The Federal regulations at 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(1) require Institutional Review Boards (IRBs) to establish a procedure for "ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head, of any unanticipated problems involving risks to subjects or others...". The FDA IND regulations at 21 CFR 312.66 also require the investigator "to assure that he or she promptly report to the IRB all unanticipated problems involving risk to human subjects or others...". In addition, 21 CFR 312.32(c) requires the sponsor to notify "all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected".

In accordance with Federal regulations, the Hebrew SeniorLife Institutional Review Board (HSL IRB) has established the following policies and procedures for the reporting of adverse events to the HSL IRB as a means of ensuring that (i) the relationship of the risks and benefits to subjects participating in research studies remains acceptable throughout the conduct of the study; and (ii) the consent document contains the information necessary for subjects to make an informed decision about their participation or continuation in a study. Adverse event reporting requirements differ by type of study and nature, severity, and relationship of the adverse event to the study procedures. The Institutional Review Board may approve exceptions to these policies and adverse event reporting guidelines on a case-by-case basis. All such exceptions will be documented in writing to the investigator.

Actions of the IRB: The IRB shall decide if urgent action is necessary to eliminate apparent immediate hazards to the participants, including the following:

- Changes to the protocol to minimize risks to participants.
- Changes to the consent form to accurately reflect the nature, frequency or severity of the event.
- Re-consenting of participants to the study.
- Placing the study on temporary hold to new enrollment and/or the study procedures discontinued because, based on the information available, the risk/benefit ratio appears unfavorable to participants.

Determinations of the IRB: The IRB shall determine appropriate action in response to the report, including one or more of the following:

- Deciding that no further action is necessary (the research may continue).
- Requiring further investigation by a member or outside expert designated by the Chair prior to the next meeting of the IRB.
- Requiring that additional information regarding risks be given to participants.
- Suspending approval
- Terminating approval

The HSL IRB shall send the PI written notice of any action taken by the IRB and the reasons for that action within five (5) working days of the IRB meeting.

Necessary notifications: PIs are required to notify their funding agency, any other IRB reviewing the protocol, and their DSMB (if they have one) of serious adverse events. Serious adverse events will be reported to the Director of the Office of Compliance at the Office of Human Research Protections (OHRP) by the IRB Administrator.