Guidance for Reporting Adverse Events, Non-Adverse Event Incidents, and Updated Study Information

OVERVIEW
The IRB requires reporting of Adverse Events, Incidents, and Updated Study Information in order to monitor for Unanticipated Problems.

Unanticipated Problems may take the form of an adverse event, incident (non-adverse event), and updated study information. Some, but not all, adverse events, incidents, and updated study information meet the criteria of an unanticipated problem.

DEFINITIONS
Adverse Event (AE): any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research.

External Adverse Event: An event or outcome that is experienced by subjects enrolled at study sites in multicenter clinical trials under the jurisdiction of external Institutional Review Boards (IRBs).

Internal Adverse Event: An event or outcome that is experienced by subjects enrolled at study sites under the jurisdiction of the SJH IRB (where SJH IRB is the IRB of record).

Incident (Non Adverse Event): An undesirable and unintended event or outcome involving any aspects of the research study that is not an adverse event.

Safety Information: Study Information that addresses the risks or potential benefits of the research study.

Serious Adverse Event: Any adverse event that: 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 a persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; or based upon 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 Problem: Any incident, experience or outcome that is (i) unexpected, (ii) related or possibly related to participation in the research, and (iii) suggests that the research places subjects or others at a greater risk of harm than previously known or recognized.

CONCEPTUALIZING UNANTICIPATED PROBLEMS
Unanticipated Problems
For an event to meet the criteria of an unanticipated problem, it must be (i) unexpected, (ii) related or possibly related to the research study, and (iii) place the subjects or others at a greater risk of harm than previously known or recognized.
• An event may be considered “unexpected” in terms of nature, severity and frequency, if (1) it is not listed in the current protocol, investigator’s brochure, consent form, or other relevant sources of information such as product labeling and package inserts; or if (2) it is not characteristic of the subject population being studied and it is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject, and the subject’s predisposing risk factor profile.

• An event is “related or possibly related” if it may have been caused by the procedures involved in the research. Incidents (including adverse events) may be caused by one or more of the following: (1) procedures involved in the research; (2) an underlying disease, disorder, or condition of the subject; or (3) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.
  o If an event is caused at least partially by (1), then the event should be considered related to participation in the research.
  o Events caused solely by (2) or (3) would be considered unrelated to participation in the research and are not reportable.

SJH considers an event possibly related if there is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research. Inability to rule out the study drug/device should not deem an event as possibly related to the research.

• An event places the subjects at a “greater risk of harm than previously known or recognized” if the event is: (i) a serious adverse event, (ii) adverse event occurring at a higher frequency or severity than initially identified, or (iii) incident that compromises the subject’s safety, privacy, or confidentiality.

The diagrams below provide a schematic of how to conceptualize Unanticipated Problems:
PROCEDURES
For studies under the jurisdiction of the SJH IRB, the Principal Investigator (PI) must report events that constitute unanticipated problems to the SJH IRB. For studies under the jurisdiction of the NCI CIRB, the PI must report events that constitute unanticipated problems to the NCI CIRB.

The procedures listed in this guidance document pertain to reporting requirements to the SJH IRB. For guidance on reporting to the NCI CIRB, please refer to the NCI CIRB website at www.ncicirb.org.

Adverse Events
All internal and external adverse events that occur on studies for which SJH IRB has oversight and that meet the criteria of an Unanticipated Problem, must be reported to the IRB as follows:

i. Unanticipated study-related deaths or life-threatening events are to be reported to the HRPP Office within 24 hours after awareness by email, and within 5 business days on the Adverse Event/Non Adverse Event Incident Report;

ii. All other reportable adverse events are to be reported within 5 business days on the Adverse Event/Non Adverse Event Incident Report; and

iii. Serious adverse events that do not meet the criteria of an Unanticipated Problem must be reported to the IRB at the time of continuing review on the SAE Summary Log only if the study is a treatment protocol and is not overseen by a central Safety Monitoring committee.

The investigator is expected to review all external events in order to make a determination of whether an event qualifies as an Unanticipated Problem. External adverse events that do not meet the reporting requirement of an Unanticipated Problem are not reportable to the IRB.

Reports of adverse events that occur on studies for which SJH IRB has oversight that do not meet the definition of an Unanticipated Problem, can be submitted to the HRPP Office if required by the sponsor with a signed letter from the Principal Investigator attesting to the fact that he or she reviewed the reports and determined that the reports do not meet the SJH reporting requirements of an Unanticipated Problem. The HRPP Office will provide the investigator an acknowledgement letter as confirmation of receipt for file.

Incidents (Non Adverse Events)
All Incidents that meet the definition of an Unanticipated Problem must be reported to the IRB within 5 business days on the Adverse Event/Non Adverse Event Incident Report

Examples of Incidents (Non Adverse Events) include, but are not limited to the following:

- any complaint of a study subject that indicates an unexpected risk, or where the complaint cannot be resolved by the research staff;
- any breach of confidentiality or privacy;
- incarceration of a study subject in a study that is not approved to enroll prisoners;
- loss of adequate resources to support continued research activities;
• members of a group result in stigmatization and discrimination in insurance and employment (e.g., biomedical research with tissues or genetics; comparing IQ of various racial groups); or
• an unexpected natural disaster, such as an earthquake, that destroys records or disrupts scheduling.

Updated Study Information

Updated Study Information that addresses the risk or potential benefits of the research, and holds, suspension or termination of research imposed by the study sponsor, investigator, funding agency, or regulatory agencies must be reported to the IRB within 5 business days on the Study Information Report.

All study related information that does not address the risk or potential benefits of the research and that does not affect the safety and welfare of subjects should be submitted to the IRB within a reasonable timeframe, or as required by the sponsor.

Examples of study information include, but are not limited to the following:

• Data Safety Monitoring Board (DSMB) reports;
• Audit or Monitoring reports;
• Follow up information on previously report Unanticipated Problem;
• FDA Safety Alerts;
• Sponsor letters; Sponsor Annual Reports
• Publication in literature;
• Investigator’s Drug/Device Brochures;
• Notification of any change in the study status;
• Changes in the FDA labeling or withdrawal from marketing of a drug, biologic, or device used in a research protocol; or
• Any information that requires prompt reporting according to the protocol or the study sponsor.

The following tables provide an overview of the reporting requirements to the SJH IRB.

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<thead>
<tr>
<th>WHAT</th>
<th>HOW</th>
<th>WHEN</th>
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<tbody>
<tr>
<td>Internal Serious Adverse Events (SAEs) that are not Unanticipated Problems (occurring on treatment studies NOT using a central safety monitoring committee)</td>
<td>SAE Summary Log</td>
<td>At Continuing Review</td>
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<tr>
<td>Updated Study Information that does not affect the safety and welfare of subjects</td>
<td>On the Study Information Report and submit to the HRPP Office</td>
<td>Within a reasonable time frame or as required by the sponsor</td>
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What, How and When to Report Events that ARE Unanticipated Problems

<table>
<thead>
<tr>
<th>WHAT</th>
<th>HOW</th>
<th>WHEN</th>
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<tr>
<td>All Unanticipated Problems (in the form of adverse events and incidents)</td>
<td>On the Adverse Event/Non Adverse Event Incident Report and submit to the HRPP Office</td>
<td>Within 5 Business Days</td>
</tr>
<tr>
<td>Updated Study Information that addresses the risks or potential benefits of the research</td>
<td>On the Study Information Report and submit to the HRPP Office</td>
<td>Within 5 Business Days</td>
</tr>
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IRB REVIEW PROCESS
Upon receipt of an Adverse Event/Non Adverse Event Incident Report, HRPP will send the report, protocol, consent form, and Investigator’s Brochure, as applicable, to the IRB Chair(s) or designated IRB member for review. The IRB Chair(s) or IRB member may request any additional information in order to appropriately evaluate the event.

If the IRB Chair(s) or IRB member determines that the event does not meet the criteria of an unanticipated problem that requires reporting, then an acknowledgement of review will be provided and no further action is required. This event will not be placed on an IRB meeting agenda and the information will be filed accordingly in its study folder.

If it is determined that the event should be reviewed by a full IRB, then the report, additional information received, protocol, consent form, and Investigator’s Brochure, as applicable, will be reviewed in the next meeting, unless otherwise specified by the Chair(s).

IRB Actions
After review of an event, the full IRB may take one or more actions. The following are a list of possible actions; however, additional actions may be recommended as applicable:

- No further action is required
- The event does not constitute an unanticipated problem and/or serious or continuing noncompliance
- The event appears to constitute an unanticipated problem and/or serious or continuing noncompliance
- Require modifications to the informed consent
- Require modifications to the protocol when permissible
- Require the investigator to re-consent enrolled subjects
- Notification of previously enrolled and/or currently enrolled subjects of new information
- Increase monitoring of subjects
- Increase frequency of continuing review
- Observation or monitoring of the research
- Require additional training and education
- Suspension of all or parts of the research
- Termination of the research
• Refer to the appropriate institutional entity

After review by the full IRB, the IRB will indicate their determination in writing to the investigator within a reasonable timeframe, but no later than 10 business days of the determination.

When the IRB determines that an unanticipated problem or serious or continuing noncompliance has occurred, or when the IRB suspends or terminates approval of research, a report will be processed according to the SJH guidance *Mandated IRB Reporting to Institutional Officials and External Agencies*.

**RESOURCES**

- **OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events**
- **FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting Improving Human Subject Protection**