Title: SARMC Institutional Review Board: Unanticipated Problems or Adverse Events Reporting

**Policy Statement:** Investigators are to notify the IRB of any unanticipated problems or adverse events involving risks to subjects or others that occur in research conducted under the purview of the IRB. Serious, unexpected, causally related adverse events or unanticipated problems must be reported within 3 working days of the knowledge of the event or as dictated by the protocol. Deaths must be reported within one day of the knowledge of the death regardless of attribution or whether anticipated as part of normal disease progression.

**Procedure:**

I. **Definitions:**
   A. The phrase “Unanticipated problem involving risks to subjects or others” is found but not defined in the Department of Health and Human Services (DHHS) regulations. The Office for Human Research Protections (OHRP) considers unanticipated problems, in general, to include those events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized as stated in the OHRP document “Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others”.

   B. An “Unexpected Adverse Experience” as defined by FDA regulations at 21 CFR 312.32(a) – Any adverse drug experience, 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 investigational plan or elsewhere in the current application, as amended. 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. “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.

   C. A “Serious Adverse Experience” as defined by FDA regulations at 21 CFR
Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

II. Required Reporting:

A. Internal Adverse Events
   1. For all internal serious or unexpected adverse events, the investigator must complete an Internal Adverse Event Form (available on the SARMC Research web site) within 3 working days of knowledge of the event. The report must contain a sufficient amount of information to allow the IRB to judge the impact on the overall risk/benefit ratio.
   2. The investigator should include the following information for either internal serious adverse events or serious unanticipated problems:
      a. participant identifier as required for acknowledgement;
      b. a brief description of the problem, why it occurred, the steps taken to resolve the problem and procedures implemented to avoid future problems;
      c. answer the question, “Did this problem have an effect on the risk(s) associated with the study?”;
      d. A brief review of the medical history and events leading to the adverse event;
      e. The date of the event and all protocols related to the adverse event;
      f. Grade and severity of the adverse event;
      g. Relationship of the event to research procedures/treatments;
      h. Similar, previous events observed in the conduct of the research;
      i. Outcome;
      j. Attribution – The determination of whether an adverse event is related to a medical treatment or procedure (see chart, pg. 4).
   3. If an unexpected death occurs, a verbal report should be provided to the IRB office immediately upon knowledge of the death and followed by a written report within 24 hours.

B. External (Sponsor or Cooperative Group) Adverse Events or Safety Reports:
   1. The SARMC IRB supports the Office of Human Research Protections (OHRP) guidelines advising that it is neither useful nor necessary for reports of individual adverse events occurring at unaffiliated sites enrolled in multi-center studies (external adverse events) to be
distributed routinely to local IRBs at all institutions conducting the research. Individual, unanalyzed adverse event reports from other study sites, often with limited information, do not yield useful data about the events that would enable the IRB to determine whether the event places subjects at greater risk of harm than previously known or recognized. The SARMC IRB agrees with these guidelines and does not accept submissions of external adverse event reports that relate to events occurring in subjects at research sites other than SARMC or an affiliated site. These reports must instead be submitted to the study sponsor's monitoring entity (e.g. the research sponsor, data safety monitoring board or data monitoring committee, or coordinating or statistical center) in accordance with the monitoring plan of the study protocol.

2. The local investigator should only submit external adverse event reports to the SARMC IRB if, after review by the sponsor or data safety monitoring board, the event prompts a change in the risk/benefit ratio or informed consent document for the study. These types of changes are typically reflected in a protocol amendment that must be submitted to the IRB. Any proposed changes in the consent form or research procedures resulting from the report are to be prepared/identified by the Principal Investigator and submitted with the report and an amendment form to the IRB for approval.

3. The IRB will determine whether re-consenting and/or subject notification about any new information is warranted. The investigator is notified in writing of the IRB’s determinations, even if no further action is necessary.

III. IRB Review of Adverse Events
   A. Internal Adverse Events
      1. All internal adverse events will be reviewed by the fully-convened IRB. The IRB will determine whether study changes are recommended depending on the impact of the event or problem on the overall risk/benefit ratio. If the research will continue, the IRB also determines whether a consent form revision is required and to what extent re-consenting and/or subject notification about the new information is warranted. The investigator is notified in writing of the IRB’s determinations, even if no further action is necessary.

   B. External Adverse Events/Safety Reports
      1. As stated above, the SARMC IRB does not accept submissions of external adverse event reports that relate to events occurring in subjects at research sites other than SARMC or an affiliated site. These reports must instead be submitted to the study sponsor's monitoring entity in accordance with the monitoring plan of the study protocol.
         a. Exceptions are reports that prompt a change in the risk/benefit ratio or informed consent document for the study. These types of changes are typically reflected in a protocol amendment that must be submitted to the IRB.
         b. All such reports are reviewed/acknowledged monthly by the
fully-convened IRB. The Investigator is notified in writing of the IRB’s determinations, even if no further action is necessary.

IV. Submission and Review of Data and Safety Monitoring Board (DSMB) Reports
A. Investigators are required to forward DSMB reports to the IRB upon receipt, or as dictated by the overseeing authority.
B. The IRB will review the DSMB report via full board review. The investigator is notified in writing of the IRB’s determinations, even if no further action is necessary.

V. Reporting of Adverse Events at Continuing Review and Study Closure
A. Continuing Review
1. All study specific internal adverse events that have occurred since the last continuing review, regardless of whether or not they have been previously reported, must be reported on the Research Study Reapproval form. At a minimum, you must report the event identifier along with a brief description of the adverse event.
2. The IRB reviews all events since the last continuing review report. The IRB needs to determine whether any new information has emerged, either from the research itself or from other sources, which could alter the IRB’s previous determinations, particularly with respect to risk to subjects.
B. Study Closure
1. All study related internal adverse events that have occurred since the study was first approved must be summarized on the Final Project Closure form. At a minimum, the summary should include the number of events, date it was reported to IRB, determination of causality and status of the participant(s).

VI. Adverse Event Causality Assessment Criteria

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<thead>
<tr>
<th>Causality</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Definitely</td>
<td>The adverse event is <strong>clearly related</strong> to the study drug/device/intervention.</td>
<td>The event has a sequential relationship to the administration of the drug, device and/or intervention, follows known pattern of response, and no alternative cause is present.</td>
</tr>
<tr>
<td>Probably</td>
<td>The adverse event is <strong>likely related</strong> to the study drug/device/intervention.</td>
<td>The event has a sequential relationship to the administration of the drug, device and/or intervention, follows a known or suspected pattern of response, but an alternative cause may be present.</td>
</tr>
<tr>
<td>Possibly</td>
<td>The adverse event <strong>may be related</strong> to the study drug/device/intervention.</td>
<td>The event has a sequential relationship to the administration of the drug, device and/or intervention, follows a suspected pattern of response, but an alternative cause is present.</td>
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<tr>
<td>Unlikely</td>
<td>The adverse event <strong>is probably not related</strong> to the study drug/device/intervention.</td>
<td>The event has a sequential relationship to the administration of the drug, device and/or intervention, but follows no known or suspected pattern of response, and an alternative cause is present.</td>
</tr>
<tr>
<td>Not Related</td>
<td>The adverse event <strong>is clearly not related</strong> to the study drug/device/intervention.</td>
<td>The event has no sequential relationship to the administration of the drug, device and/or intervention, follows no known response or suspected pattern of response, and an alternative cause is present.</td>
</tr>
<tr>
<td>Not Specified</td>
<td>It <strong>is not specified</strong> if the adverse event is related to the study drug/device/intervention.</td>
<td>The event has not been specified as to the causal relationship to the drug, device and/or intervention; additional information is usually being requested or reviewed; subsequent determination is usually forthcoming.</td>
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**VII. IRB Authority**

The IRB may require further information and/or clarification of the event, including a review of the occurrence in other studies using the same drug/device/intervention; notification of current research participants of the risk of the event; and/or revision of the informed consent document.

The IRB may also change the duration of the approval period, require an increase in the frequency of monitoring, and suspend the project until additional information is reviewed, or permanently stop the study. Failure to comply with timely reporting of may result in the immediate suspension or termination of a study or may impose new restrictions on a study.
It is the responsibility of the IRB Chairperson or his/her designee to provide prompt written notification to Saint Alphonsus Regional Medical Center's appropriate institutional official and to relevant federal agencies, including OHRP and FDA (for FDA-regulated research), if such changes are made due to any serious adverse event or serious unanticipated problems involving risks to subjects or others, and to inform the relevant federal agency of the resolution of those problems.

**Related Policies:** Research Policy, Continuing Review Policy; IRB Functions & Operations Policy; IRB Purpose and Authority Policy; Study Closure Policy

**Related Forms:** Internal Adverse Event Form; Research Study Reapproval Form; Final Project Closure available at [http://www.saintalphonsus.org/forms-and-resources](http://www.saintalphonsus.org/forms-and-resources)

**References:**


Office of Human Research Protections, Department of Health and Human Services (Last revised January 15th, 2007). Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.