Flow Chart for Determining Unanticipated Problems and SAEs

Adverse Event

- Expected
  - Non-Serious
    - Unrelated
    - Possibly Related or Related
  - Serious
    - Possibly Related or Related
    - Unrelated
- Unexpected
  - Possibly Related or Related
  - Unrelated

Non-Adverse Event

- Unexpected
  - Harm or Increased Risk of Harm
    - Possibly Related or Related

Non-Serious Adverse Event

Serious Adverse Event

Unanticipated Problem
# Guidelines for reporting *Unanticipated Problems* and *Adverse Events* to the Tufts MC/TUHS IRB

<table>
<thead>
<tr>
<th><strong>Unanticipated Problem (UP): Internal or External</strong></th>
<th><strong>Immediate reporting; completed SAE and Unanticipated Problem Reporting Form with supporting documents submitted to IRB within 5 business days</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAE: Internal or External, Related or Possibly Related, Unexpected</strong></td>
<td>Meets criteria for an <em>Unanticipated Problem</em> and is to be reported as such</td>
</tr>
<tr>
<td><strong>SAE: Internal, all other situations</strong></td>
<td>Complete <em>Event Reporting Form</em> and submit to IRB within 15 business days</td>
</tr>
<tr>
<td><strong>SAE: External, requiring change in protocol or ICFs but NOT considered an UP</strong></td>
<td>Complete <em>SAE and Unanticipated Problem Reporting Form</em> and submit to IRB within 15 business days</td>
</tr>
<tr>
<td><strong>SAE: External, all other situations</strong></td>
<td>Submit a summary using the <em>External SAE Summary Reporting Form</em> for all interval events 1) at the time of study Continuing Review, or 2) at the time of study termination (if before CR), or 3) as required by the IRB approved study protocol</td>
</tr>
<tr>
<td><strong>Non-Serious AE: Internal, all situations not considered an Unanticipated Problem</strong></td>
<td>Clinically significant <em>AEs</em> may be summarized at the time of Continuing Review, or study termination if before the next scheduled Continuing Review</td>
</tr>
<tr>
<td><strong>Non-Serious AE: External, all situations not considered an Unanticipated Problem</strong></td>
<td>Not required to be reported to the IRB</td>
</tr>
</tbody>
</table>
An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator’s car on the way home from work.

- **Non-Adverse Event** (no harm done – yet)
- **Unanticipated Problem**: unexpected (nature), related to study participation, results in increased risk for harm than previously recognized
  - Psychological and social harm from the breach in confidentiality
Subjects with coronary artery disease presenting with unstable angina are enrolled in a multicenter clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent. The risk of needing emergency CABG surgery is described in the IRB-approved protocol and ICF. After the first 20 subjects are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent.

- **Serious Adverse Events**
- **Unanticipated Problem:** unexpected (frequency), related to study participation, serious
As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. Fortunately, the subject does not experience any side effects, and no detectable adverse physical or laboratory abnormalities are identified.

- **Non-Adverse Event**
- **Unanticipated Problem**: unexpected (nature), related to study participation, results in increased risk for harm than previously recognized
  - Side-effects of experimental agent
A subject participating in a phase III, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent versus placebo added to standard chemotherapy treatment for multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multiorgan failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections are known complications of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and ICFs.

- **Serious Adverse Event**
- **Not Unanticipated Problem**: expected, related to study participation, **serious**
Example 5

- A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo-controlled, double-blind, phase III clinical trial evaluating an investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and ICF for the study do not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure.

- **Serious Adverse Event**
- **Unanticipated Problem**: *unexpected* (nature), *related* to study participation, *serious*
An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and ICF describe claustrophobic reactions as one of the risks of the research. The 20th subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research.

- Adverse Event
- Not Unanticipated Problem: expected, related to study participation, serious
An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, whose medical data are being collected for the registry, dies as the result of an infection that commonly occurs in the NICU setting.

- **Serious Adverse Event**
- **Not Unanticipated Problem**: expected, not related to study participation, **serious**
Subjects with cancer are enrolled in a phase II clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus.

- **Non-Adverse Event** (no harm done – yet)
- **Unanticipated Problem**: unexpected (nature), related to study participation, results in increased risk for harm than previously recognized
  - Infection risk
Example 9

- A subject with seizures enrolls in a randomized, phase III clinical trial comparing an investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and ICF for the study do not identify anemia as a risk of the research.

- **Serious Adverse Event**
- **Unanticipated Problem**: unexpected (nature), related to study participation, serious
The 5th subject enrolled in a phase II, open-label, uncontrolled clinical study evaluating the safety and efficacy of an investigational oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the investigational oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies; but, there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and ICF for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure.

- **Serious Adverse Event**
- **Unanticipated Problem**: *unexpected* (severity), *related* to study participation, *serious*
A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject’s initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, related to the underlying renal cell carcinoma.

- **Serious Adverse Event**
- **Not Unanticipated Problem**: unexpected (for the study), not related to study participation, serious