I. Introduction

This document discusses the classification and reporting requirements for adverse events and unanticipated problems that occur during the conduct of a research study involving human subjects. Reporting of these types of problems is critical to ensure human subject protections, as these are the types of problems that may require modification to the protocol/informed consent form (ICF). The policy derives from the applicable sections of 45 CFR 46, US Food and Drug Administration (FDA) regulations, including the January 2009 guidance, and the Office for Human Research Protections (OHRP), including the January 15, 2007 guidance. This policy clarifies the implementation of these regulations and guidance at Tufts Medical Center (Tufts MC)/Tufts University Health Sciences Campus (TUHS).

II. Terminology

Unanticipated Problem

Definition: An Unanticipated Problem is an incident, experience, or outcome that meets all of the following criteria:

1. The nature, severity, or frequency is unexpected for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the ICF(s).
2. It is related or possibly related to participation in the research.
3. It suggests the research may place the subject or others at a greater risk of harm then was previously recognized.

Adverse Event (AE)

Definition: An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with a subject’s participation in the research. Every AE is classified as:

1. Non-serious or Serious
2. Related (includes both definite and probable relationships), Possibly Related, or Unrelated to participation in the research.
3. Expected or Unexpected based on the known:
   a. Risks associate with drugs, devices, or other protocol activities described in the IRB approved protocol, supporting documents, and ICFs, or
   b. Natural progression of an underlying illness, or
   c. Health characteristics of the study population.
4. Internal or External depending on whether the AE occurred at a study site where the Tufts Medical Center/TUHS IRB is the responsible approving body (Internal), or the AE occurred at a research site not under the jurisdiction of the Tufts MC/TUHS IRB (External).

   a. An External AE is most often encountered with multi-center studies where the AE occurred at an outside research site having its own IRB.

**Serious Adverse Event (SAE)**

Definition: A SAE is any AE that:

1. Results in death, or
2. Is life-threatening, or
3. Results in hospitalization or prolongation of existing hospitalization, or
4. Results in a persistent or significant disability/incapacitation, or
5. Results in a congenital anomaly/birth defect, or
6. May jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

III. **Determination of whether an adverse event is an unanticipated problem**

An **Unanticipated Problem** is a major concern of an investigator and the IRB as it generally requires actions such as modification or suspension of the protocol, or informing subjects. All **three** of the criteria in the definition above must be met to be an Unanticipated Problem. This means that not all Unexpected Serious Adverse Events are Unanticipated Problems since some of them may, for example, not be related to the participation in the research study. Likewise, there does not have to be an AE to be an Unanticipated Problem.

For example, an event may be observed which is unexpected, related to participation in a study, but did not result in harm to the subject. If, however, it is determined that the subject (or others) are at an increased risk for harm, this would be an Unanticipated Problem. Unanticipated Problems do not only include risks of physical harm, but also psychological, economic, or social harm. Please see the flow chart in Appendix A for more detail, and Appendix B for specific examples.

All Unanticipated Problems must be promptly reported to the IRB. Unanticipated Problems may also require prompt reporting to the appropriate institutional officials, the study sponsor or funding source (if applicable), the FDA (for drug/biologic/device/vaccine, etc., associated events), and/or OHRP.

IV. **Reporting Requirements and Procedures, and Related Activities**

Reports, when required, must be submitted to the IRB for each event occurring for each subject **individually using the Tuft MC/TUHS IRB Event Reporting Form**. All supporting documentation must be attached to the Event Reporting Form. Reporting requirements and procedures, and related activities are described below and summarized in Table 1. A reporting plan must be included in the protocol, and must be consistent with the requirements below, unless specific modifications were approved by the IRB.

**Unanticipated Problems**

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Each **Unanticipated Problem** requires immediate action by the principal investigator (PI) as follows:

1. Immediate corrective action must be taken to eliminate or minimize risk to enrolled subjects. This could necessitate a voluntary hold on further enrollment and/or research activities for already enrolled subjects. If subjects are at immediate risk, these corrective actions must be initiated immediately, and if necessary for subject safety, simultaneous with completion of reporting requirements. In such an instance, the PI should immediately call the IRB office.

2. Enrollment of new subjects should be voluntarily stopped until a revised protocol and/or ICF(s) are reviewed and approved by the Tufts Medical Center/TUHS IRB. In some situations enrollment may continue, provided new subjects are not at risk, and the PI provides the IRB the necessary documentation in support of continuation of enrollment. It may also be necessary for the IRB to formally suspend a study under certain conditions.

3. The problem must be promptly reported to the Tufts Medical Center/TUHS IRB, the study sponsor, and all data monitoring entities involved with the study.
   
   a. An initial report to the Tufts MC/TUHS IRB must be submitted in writing no later than two (2) business days after the PI/study team become aware of the problem. This report is to briefly summarize the nature of the event, summarize the corrective action plan as developed and initiated at that time, and clarify whether subject enrollment is continuing. In the rare circumstance where an original written report cannot be submitted directly to the IRB office, it may be faxed within 2 business days (617-636-8394). The IRB office may be contacted by phone at 617-636-7512 for necessary guidance, and PIs are encouraged to do so.
   
   b. An **Event Reporting Form** must be completed with accompanying documentation addressing each item in this list and submitted to the Tufts MC/TUHS IRB no later than five (5) business days after the PI/study team became aware of the problem.
   
   c. A report must also be filed with the FDA for studies using investigational drugs and devices, or where the **Unanticipated Problem** is deemed related or possibly related to an approved drug or device used in the study. (More information may be obtained at [http://www.fda.gov/medwatch/how.htm](http://www.fda.gov/medwatch/how.htm). Reporting is typically done by the individual or entity to whom the IND or IDE has been issued and is to be in conformity with the agency’s reporting requirements.

**Note 1:** Like AEs, Unanticipated Problems may be Internal or External, but unlike AEs, BOTH Internal and External Unanticipated Problems must be reported according to the requirements outlined above.

**Serious Adverse Events (SAE)**

Reporting requirements vary for SAEs as follow:

1. A SAE that is Related or Possibly Related and Unexpected meets criteria for an **Unanticipated Problem** and should be acted upon as outlined above.
   
   a. This applies to both Internal and External SAEs.
   
   b. A completed **SAE/UP Reporting Form** with all necessary supporting documents must be submitted to the Tufts Medical Center/TUHS IRB within five (5) business days of the PI/research team learning of the event.
2. An Internal SAE not meeting criteria for an Unanticipated Problem must be reported to the Tufts Medical Center/TUHS IRB within fifteen (15) business days of the PI/research team learning of the event; the SAE/UP Reporting Form must be used.
   a. If changes are required to the protocol and/or ICF(s), subject enrollment and study activities related to the AE, and not necessary for subject safety, cannot continue until the changes have been reviewed and approved by the Tufts Medical Center/TUHS IRB.

3. An External SAE not meeting criteria of an Unanticipated Problem, but requiring changes to the protocol and/or ICFs must be reported to the Tufts Medical Center/TUHS IRB within fifteen (15) business days of the PI/research team learning of the event. The report is to be made using the SAE/UP Reporting Form.
   a. Subject enrollment and study activities related to the AE, and not necessary for subject safety, cannot continue until the changes have been reviewed and approved by the Tufts Medical Center/TUHS IRB.

4. An External SAE not meeting criteria of an Unanticipated Problem, and not resulting in changes to the protocol an/or ICF(s) are to be summarized and submitted to the Tufts MC/TUHS IRB for review by using the Summary Reporting Form at the time of continuing review, or as required by the IRB approved study protocol.

Non-serious Adverse Events

1. All clinically significant Internal Non-serious Adverse Events not meeting criteria of an Unanticipated Problem can be summarized and submitted to the Tufts Medical Center/TUHS IRB at the time of the continuing review, or when the PI terminates the study if this occurs before the date of the next continuing review.

2. All Non-serious External Adverse Events not meeting criteria for an Unanticipated Problem do not need to be reported to the Tufts Medical Center/TUHS IRB.

Table 1. Guidelines for reporting Unanticipated Problems and Adverse Events to the Tufts MC/TUHS IRB.

| Unanticipated Problem: Internal or External | Immediate reporting as described above  
|                                             | Completed SAE/UP Reporting Form with supporting documents submitted to IRB within 5 business days  

| SAE: Internal or External, Related or Possibly Related, Unexpected | Meets criteria for an Unanticipated Problem and is to be reported as such  

| SAE: Internal, all other situations | Complete SAE/UP Reporting Form and submit to IRB within 15 business days  

| SAE: External, requiring change in protocol or ICFs but NOT considered an Unanticipated Problem. | Complete SAE/UP Reporting Form and submit to IRB within 15 business days  

| SAE: External, all other situations | Submit a summary using the Summary Reporting Form all interval events 1) at the time of study Continuing Review, or 2) at the time of study termination if before the next scheduled Continuing Review, or 3) as required by the IRB approved study protocol  

| Non-Serious AE: Internal, all situations not considered an Unanticipated Problem | Using the Summary Reporting Form for clinically significant AEs may be summarized at the time of Continuing Review, or study termination if before the next scheduled Continuing Review  

| Non-Serious AE: External, all situations not considered an Unanticipated Problem | Not required to be reported to the IRB  

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V.

Responsibilities of the Investigator

A. All greater than minimal risk protocols are to include a delineation of an action plan for all Unanticipated Problems and Serious Adverse Events (SAEs), including clarification about to whom the events will be reported, such as the IRB, federal agencies, sponsor (if applicable), and the specific reporting timeframes. Statements such as “Adverse events will be reported as per local IRB guidelines” are not adequate. Investigators may propose modifications to these guidelines as appropriate to the protocol; but, the modifications must be approved by the IRB prior to implementation. The PI should propose modifications to the standard reporting plan both in instances where shorter reporting timeframes may be necessary (for example, particularly vulnerable populations or potentially controversial research interventions) or longer (for example, deaths in a minimal risk study in a high risk population where the deaths are likely to be from the underlying disease and not the minimal risk research intervention). If relevant, the plan should also have provision for who will review and submit event reports in the PI’s absence. If the PI cannot modify the main protocol document, the reporting plan is to be outlined in a Site Specific Appendix.

Protocols may contain their own assessment scales for judging the severity of an AE. Typical scales may range from 1 (mild) to 5 (fatal). While these scales may be useful in study analysis, it is important that the PI use the criteria in the Terminology section above to determine if an AE is Serious or Non-Serious for purposes of assessing subject risk and meeting the reporting requirements set forth in this document.

B. The PI must comply with all reporting requirements noted above. The PI must provide sufficient information to allow the IRB to make an assessment of risk. The IRB may request additional information from the PI. When requested, the PI is expected to provide this additional information within two (2) business weeks, or sooner if specified by the IRB. If the PI determines that an event is study related or possibly study related, but does not feel that changes to the ICF and/or protocol are necessary, a rationale is to be provided within the timeframe specified by the IRB.

C. The PI must independently begin initiation of corrective action plans necessary to ensure subject safety while preparing and submitting the required reports.

D. The PI must provide all reports from Data and Safety Monitoring Boards (DSMBs) and other data/safety monitoring committees relevant to the interpretation or follow-up of Unanticipated Problems and Serious Adverse Events. Actions by data/safety monitors to change the conduct of a trial must be reported to the IRB within seven business (7) days of receipt by the PI. The PI should provide an interim plan for the conduct of the trial while necessary amendments are being prepared. All reports from data/safety monitors must be submitted at time of initial study submission for studies that are ongoing at other sites. All reports obtained after the initial Tufts Medical Center/TUHS IRB approval, or last continuing review, should be submitted at the next scheduled continuing review application.

E. A summary of all Adverse Events and Unanticipated Problems since the initial protocol approval, or last continuing review, must be submitted with the next scheduled continuing review application. The PI is to assess at that time whether when reviewed in combination, further changes to the protocol and/or ICF may be necessary that were not identified at the time they were individually reported.

VI. Responsibilities of the IRB

The IRB must ensure that research includes adequate provisions for monitoring the data collected to ensure the safety of subjects.

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1. The IRB *does not* conduct the monitoring, but may request, where appropriate, additional monitoring to be performed.
   a. The IRB has the authority to:
      i. Determine the type of data or events that are to be captured under the monitoring provisions.
      ii. Request that a data monitor be established for any research.
      iii. Request additions or changes to the monitoring entity proposed for the research.
      iv. Have a third party observe the research.

2. The IRB may determine:
   a. The timeframes for reporting adverse events and unanticipated problems to the monitoring entity.
   b. The frequency of assessments of data or events captured by the monitoring provisions.
   c. The definition of specific triggers or stopping rules that will dictate when an action is required.
   d. Procedures for communicating to the IRB(s), study sponsor, study investigator(s), and other appropriate officials the outcome of the reviews by the monitoring entity.

A. The IRB is responsible for reviewing all reported *Adverse Events* and *Unanticipated Problems* submitted by the PI.

1. Sufficient information must be reported to the IRB so that a determination of risk to study subjects can be made.
   a. The IRB has the authority to request changes in the protocol and/or ICF(s) as the result of *Adverse Events* or *Unanticipated Problems*

B. The IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

1. The IRB must review the summary of information provided by the PI of:
   a. *Unanticipated Problems*
   b. *Adverse Events*
   c. New findings that may be relevant to the research
   d. Data monitoring reports.

2. The IRB may request changes to the protocol, ICF(s), and data monitoring based on all information available at the time of continuing review. In reviewing the continuing review, the IRB’s focus will be to determine if the information reviewed in combination requires additional changes to the conduct of the study or ICF that was not evident when the events were reported individually.

3. For multi-center studies already ongoing at other sites, the IRB must review a summary of the same information at time of initial review.

C. The IRB may:

1. Recommend the suspension or termination of a study for investigator non-compliance or unanticipated problems. See institutional Suspension and Termination Policy.
2. Recommend the reporting by Tufts MC/TUHS Institutional Official to OHRP, FDA, National Institutes of Health (NIH), or other governance or funding agency, study non-compliance or *Unanticipated Problems*.

D. IRB procedure

1. Preliminary review: Upon receipt of an *Event Report* in the IRB office, it will be reviewed by the office staff for completeness. Incomplete reports will be returned to the PI for the required missing information. Reports will typically be directed to the Chair, Vice-Chair, or earliest available designated reviewer. For *Unanticipated Problems* and *Events* of special concern, the Chair or acting Chair will be contacted and the report brought to his/her immediate attention.

2. Review: *Event Reports* will be reviewed by an IRB member. This will be done typically by the Chair or Vice-Chair or member designated by the Chair.

3. Upon review of an *Event Report*, the reviewer will decide if action is necessary to minimize any potential risk(s) to the former, current, and/or future subjects. Actions taken may include:

   a. Acknowledge the report, with no changes to the ICF and/or protocol necessary.
   b. Request additional information for clarification.
   c. Request changes to the ICF and/or protocol in response to the report.
   d. Refer the report to the Chair.
   e. Approve accompanying ICF and/or protocol changes submitted by the PI in response to the report, provided the reviewer determines that the modifications constitute “minor changes” as per 45 CFR 46.110.
   f. After ensuring that appropriate measures are put in place to ensure subject safety, refer to the next convened IRB meeting any ICF and/or protocol changes that do not qualify as “minor changes”; a reported event determined to significantly adversely alter the overall risk/benefit profile may be referred to the convened IRB meeting to determine if additional ICF and/or protocol changes are required.
   g. Subjects may be required to sign a revised or addendum ICF communicating the new information. The new information may also need to be reported to subjects who have completed their participation in the study.
   h. The research study may be temporarily suspended and/or the research study procedures discontinued/terminated.
   i. The research study may be suspended or terminated in accord with the institutional “Involuntary Suspension/Termination of Research Protocols and Suspension/Termination Reporting” section of the IRB operations manual.

4. The event reviewer will document his/her determination in writing on the *Event Report* cover sheet. Written documentation, including any communication with the PI regarding the *AE*, will be kept in the IRB file.
Appendix

A. Flow chart of reporting categories.

Flow chart showing various relationships between Events (Adverse and Non-Adverse) and Event Reporting categories. Note that “Non-Adverse Events” themselves do not constitute a specific reporting category, but they may include unexpected situations that place subjects at increased risk for harm. If such situations are deemed related, or possibly related to participation in the research study, they would be categorized as Unanticipated Problems.
B. Examples of Unanticipated Problems; modified from the OHRP (http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm)

1. Unanticipated Problems that are not Adverse Events (i.e. Non-Adverse Events)
   a. 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. This is not an Adverse Event since no harm to participants has been identified at the time the laptop is discovered to be missing. This event does, however, place the subjects at a greater risk, than previously known, of psychological and social harm from the breach in confidentiality of the study data. Since this Non-Adverse Event was also unexpected and related to participation in the study, all criteria are met for an Unanticipated Problem: unexpected, related to study participation, serious (results in increased risk for harm than previously recognized).

   b. 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. The study subject was, however, placed at increased risk of harm so this is a Non-Adverse Event with an increased risk of harm from drug toxicity than was previously recognized. The pharmacy error was unexpected so this constitutes an Unanticipated Problem: unexpected, related to participation in the study, serious (increased risk of harm than previously recognized).

   c. Subjects with cancer are enrolled in a phase 2 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. This constitutes an unanticipated problem that must be reported because the incident was unexpected, related to participation in the research, serious (placed subjects and others at a greater risk of physical harm than was previously known or recognized).

1. Adverse Events that are non-serious (i.e. Non-Serious Adverse Events) but that are Unanticipated Problems
   a. Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have recurrent symptoms of GERD that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an Adverse Event that, although not serious, represents an Unanticipated Problem because it was unexpected in nature, possibly related to participation in the research, and suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.
b. A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject’s negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an Unanticipated Problem because, although not serious, the Adverse Event was unexpected, related to participation in the research, and suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

2. Serious Adverse Events that are not Unanticipated Problems

a. 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. The investigators conclude that the subject’s infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency. This example is a Serious Adverse Event that is not an Unanticipated Problem because the occurrence of severe infections and death in terms of nature, severity, and frequency was expected.

b. 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 twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This is a Serious Adverse Event that is not Unanticipated Problem because the occurrence of the claustrophobic reactions in terms of nature, severity, and frequency was expected.

c. 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, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject’s death is unrelated to participation in the research. Thus, this is a Serious Adverse Event that is not an Unanticipated Problem because the subject’s pulmonary embolus and death were attributed to causes other than the research interventions.
d. 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. This is a Serious Adverse Event that is not Unanticipated Problem because the death of the subject is not related to participation in the research, but is most likely related to the infant’s underlying medical condition.

3. **Serious Adverse Events that are Unanticipated Problems**

a. A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo-controlled, double-blind, phase III clinical trial evaluating a new 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. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is a Serious Adverse Event that is an Unanticipated Problem because the subject’s acute renal failure was unexpected in nature, related to participation in the research, and serious.

b. 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 informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is a Serious Adverse Event that is an Unanticipated Problem because the hematologic toxicity was unexpected in nature, possibly related to participation in the research, and serious.

c. The fifth 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 in this subject and determine it is possibly due to the study agent. This is a Serious Adverse Event that is Unanticipated Problem because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was unexpected in severity, possibly related to participation in the research, and serious.

d. 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. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the investigators. Each of the cases of emergency CABG surgery is a *Serious Adverse Event*, and each would have needed to be reported to the appropriate local IRBs, the study sponsor, other appropriate agencies, and the DSMB for the study. As a result of the DSMB assessment, these *Serious Adverse Events* have now become identified as *Unanticipated Problems* because the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency (an *unexpected* outcome), and these *SAEs* were *related* to participation in the research.