EXAMPLE SCENARIOS OF UNANTICIPATED PROBLEM INVOLVING RISK TO SUBJECTS OR OTHERS

1) Any incident experience or outcome that was not expected by the submitted protocol documentation or exceeded the frequency or severity expected in the subject population, and is definitely or probably related and is a serious adverse event.

2) Any incident experience or outcome that was not expected by the submitted protocol documentation or exceeded the frequency or severity expected in the subject population, and is definitely or probably related and although not a serious adverse event, suggests the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

3) Any incident experience or outcome that was not expected by the submitted protocol documentation or exceeded the frequency or severity expected in the subject population, and is definitely or probably related and although it did not directly result in a physical or psychological harm, suggests the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

4) A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.

5) A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.

6) Multiple occurrences of an adverse event that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.

7) An adverse event that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator’s brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.
8) A serious adverse event that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). We recommend that a discussion of the divergence from the expected rate accompany the report.

9) Any other adverse event or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator’s brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

10) Information indicating a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:

   1. An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
   2. Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
   3. A paper is published from another study that shows that an arm of your research study is of no therapeutic value.

11) Unanticipated adverse device effect (1) Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or 2) any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)

12) Breach of confidentiality.

13) Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

14) Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.

15) Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

16) Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
17) Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the PI placed one or more participants at increased risk, or affects the rights or welfare of subjects.