

Adverse Events

External adverse events are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction.

Internal adverse events are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

Comprehensive Adverse Events List

For an investigational agent, please include a comprehensive list of all reported adverse events and any potential risks for each agent (such as the toxicities seen with another agent of the same class or risks seen in animals administered this agent) as provided by the manufacturer/CAEPR. Please also include the recommended treatment for the commonly occurring events. This information may be provided in tabular format.

For a commercial agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the package insert(s) for the comprehensive list of adverse events. Please also include the recommended clinical management for the commonly occurring events. This information may be provided in tabular format.

Example:

Adverse Event (severity)	Action on Study Drug	Recommended clinical management

Grades of Event

The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

Serious Adverse Events (SAE's)

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm³ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations. . However, some protocols specifically state that certain SAEs do not require expedited reporting (such as grade 4 neutropenia in a leukemia trial). This may also be included for protocol specific SAE reporting.

Reporting SAE's

SAEs will be recorded on the FDA Form 3500A (MedWatch) if applicable (see FDA reporting requirements below).

FDA Reporting Requirements (IND studies only)

- The Sponsor-Investigator will be responsible for reporting applicable SAE's to the FDA.
- All SAEs must be reported to the FDA using FDA Form 3500A (MedWatch)
- All SAEs must be reported via fax to the CDER review division that has responsibility for review of the IND.
 - 7-day safety reports must be submitted to the FDA review division that has responsibility for the review of the IND.

- **Fatal or Life Threatening AND Unexpected AND Suspected to be RELATED** to the investigational product must be reported no later than 7 calendar days after the sponsor-investigator's receipt of the information.
- **Serious AND Unexpected AND Suspected to be RELATED** to the investigational product must be reported no later than 15 calendar days after the sponsor-investigator's receipt of the information
- Events occurring at higher rate (i.e. expected) than anticipated that are both **Serious** and Suspected to be **RELATED** to the investigational product must be reported no later than 15 calendar days after the sponsor determines the results from the aggregate analysis of the specific events qualifies for reporting
 - FDA considers an aggregate analysis of specific safety events reportable if the results of the analysis indicate the events are occurring more frequently in the drug treatment group than in the control group (if the study does not contain a control group, historical controls maybe referenced).
- Findings from animal / in vitro / epidemiological studies that suggest a significant risk to human subjects no later than 15 calendar days after the sponsor's receipt of the information
- Any relevant additional information must be submitted to the FDA (i.e. IND Follow Up Safety Report).