

ADVERSE EVENT DEFINITIONS

- A. Definitions pertaining to Serious and Unexpected Adverse Events (SAE) resulting from research with investigational drugs:
1. Adverse Event (AE). An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
 2. Serious Adverse Drug Experience. 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 an 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).
 3. Unexpected Adverse Drug Experience. 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 (21 CFR 312.32).
 4. Serious and Unexpected. Any event that occurs during a subject's participation in the study that meets the criteria established in the 21 CFR 312 definitions for both serious and unexpected. Note that events not associated with participation in the

study, e.g., those that occur after screening, but before administration of a test article, would not be considered serious and unexpected (21 CFR 312.60).

5. Investigational New Drug (IND) Safety Report. As required by 21 CFR 312.55, sponsors of IND research are required to “keep each participating investigator informed of new observations discovered by or reported to the sponsor on the new drug, particularly with respect to adverse effects and safe use.”
6. Unanticipated Adverse Device Effect. An unanticipated adverse device effect means 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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3).

B. Definitions pertaining to Serious and unexpected adverse events resulting from research not regulated by the Food and Drug Administration.

1. In accordance with 32 CFR 219, as a condition of receiving an assurance of compliance, Institutional Review Boards (IRBs) will have “written procedures for ensuring prompt reporting to the IRB, and appropriate CG officials, of any unanticipated problems involving risks to subjects or others.” AEs that are serious or unexpected as identified within the context of the FDA definitions qualify as unanticipated problems. Therefore, any event that results in death, a life-threatening experience, inpatient hospitalization or prolongation of an existing hospitalization, a persistent or significant disability /incapacity, or a congenital anomaly/birth defect qualify as an SAE. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the research participant and may require medical or surgical intervention. Examples of unanticipated problems that qualify as SAEs follow:
 - (a) In research involving an exercise intervention, events resulting in lost time from work or a limitation in the ability of the participant to perform normal daily activities (e.g., a muscle strain in the back).
 - (b) In research involving active duty military personnel, events that result in a temporary or permanent profile.
 - (c) In research involving personal or telephonic interviews, a suicidal ideation expressed during an interview.
 - (d) In outcomes research in disease management in which there is no direct intervention, events that have not been previously observed in participants taking part in this or similar research qualify as SAEs. Hospitalization for

sequelae of the disease under observation, if identified as an outcome variable in the study design and coordinated in advance with the IRB and HSRRB with regard to the regular reporting of events, would not be an SAE. Deaths from the disease under investigation, however, are reportable as SAEs.

- (e) For drug or device research involving FDA approved products not subject to regulation under 21CFR 312 or 21 CFR 812, SAEs refer to adverse events not described in the approved product labeling or events occurring at a greater frequency than the approved product labeling (21 CFR 314.80).

NOTE: The CG requires reporting of serious and unexpected adverse events. In addition, the continuing review report submitted to the IRB of record will contain a compilation of all adverse events and the respective outcomes associated with the product during the course of the year. A sample form for reporting serious and unexpected adverse events can be found on the Commandant (CG-113) website <http://www.uscg.mil/hq/cg1/cg113/default.asp>).