Tool Summary Sheet: Safety Definitions for Clinical Research

**Purpose:** To provide definitions of important safety terminology for educational purposes. Terminology may be used for protocol development when a protocol template with sample language is not already available.

**Audience/User**
Investigators, site staff, data coordinating staff, statisticians

**Details**
This tool provides definitions, references, and additional guidance associated with safety terminology

**Best Practice Recommendations**
- When using these definitions during protocol development, ensure the protocol includes definitions of safety terms that are most relevant to the nature of the protocol.
- Even ICH/CFR standard definitions of adverse events and serious adverse events may be modified, as long as those modifications are approved by the governing IRB/IEC and regulatory body, as required. For example, in a patient population that is regularly hospitalized, an event may be considered serious only if the hospitalization is > 4 days.
- In the document, the instructional text is indicated by *blue italics* ("CROMS_Instruction" style).

**References**
Office for Human Subjects Protection, Division of Department of Health and Human Services Policy; “Unanticipated Problems Involving Risks and Adverse Events Guidance” (2007)

Code of Federal Regulations Title 21, Part 312.32 (2016)

**Tool Revision History:**

<table>
<thead>
<tr>
<th>Version Number</th>
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<th>Summary of Revisions Made</th>
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<tbody>
<tr>
<td>1.0</td>
<td>26Apr2010</td>
<td>First approved version</td>
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<tr>
<td>2.0</td>
<td>28Mar2013</td>
<td>Added Tool Summary Sheet, unanticipated problems, references, and details</td>
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<tr>
<td>3.0</td>
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<td>Updated Tool Summary Sheet, content, and references to reflect ICH E6 (R2) dated Nov2016</td>
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SAFETY DEFINITIONS FOR CLINICAL RESEARCH

1 UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. suggests that 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.

{Per the definition, only a subset of adverse events would be characterized as unanticipated problems. There are other types of incidents, experiences and outcomes that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).}

2 ADVERSE EVENTS

2.1 Definitions

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. [From ICH E2A and E6, “investigational” term only in E6]

- An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. [From OHRP Guidance]
• **Adverse event** means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. [From CFR 312.32]

2.2 **Categories of Adverse Events**

• **Adverse Drug Reactions**
  In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). [From ICH E6]

• **Unexpected Adverse Drug Reaction**
  An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). [From ICH E6]

• **Suspected adverse reaction** means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. [From CFR 312.32]

• **Unexpected adverse event or unexpected suspected adverse reaction.** An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, 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 referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral
vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. [From CFR 312.32]

- **Treatment Emergent Adverse Event**
  An AE for which the start date is on or after the date that the intervention began.

- **Serious Adverse Events**
  SAEs are a subset of adverse events.
  
  An SAE is defined as any untoward medical occurrence that meets any of the following criteria:
  
  - results in death
  - is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. [Explanatory text from ICH E2A])
  - requires inpatient hospitalization or prolongation of existing hospitalization
  - results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect  [Bullets 1-5 from ICH E2A and E6]

  In addition, an important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [Adapted from OHRP Guidance]

  **{Some protocols may list events specific to the protocol that should be reported as serious. Examples might be post-extraction bleeding in anticoagulated participants and anaphylactic reaction after lidocaine or analgesic administration.}**

  An adverse event or suspected adverse reaction is considered "**serious**" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in
death, be life-threatening, or require hospitalization may be considered serious 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. [From CFR 312.32]