

## Adverse Event Terminology

By Norman M. Goldfarb

In clinical studies, an adverse event consists of any unfavorable medical occurrence in a subject, whether or not expected. It can be a new or worsening symptom or disease. It can be caused by the study or be unrelated to the study. However, relatedness can be tricky to determine; for example, a study drug might cause dizziness, which, in turn, causes a household accident.

The term "adverse" appears in 163 documents in First Clinical Research Laws, Regulations and Guidelines.<sup>1</sup> (In comparison, the term "informed consent" appears in 159 documents.) Adverse events are a subject of great concern for human subjects protection and the safety profile of an experimental drug or device. It is therefore no surprise that there are numerous adverse event terms.<sup>2</sup>

### Adverse Event Definitions

The following documents provide definitions of "adverse event" and related terms, as presented in the following categories:

- U.S. Drug Regulations
- ICH Guidances
- Unanticipated Problems
- U.S. National Cancer Institute Guideline
- Medical Device Regulations, Guidance and ISO Guideline
- European Directive and Guidelines
- Other

### U.S. Drug Regulations

Three parts of the U.S. Code of Federal Regulations define adverse event terms in connection with clinical studies of drugs.

#### **21 CFR 312. Investigational New Drug Application<sup>3</sup>**

21 CFR 312 applies to studies conducted under an Investigational New Drug Application (IND). 21 CFR 312 defines the following terms:

**Adverse event** means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

**Life-threatening adverse event or life-threatening suspected adverse reaction.** An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

**Serious adverse event or serious suspected adverse reaction.** 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.

**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.

**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.

## **21 CFR 314. Applications for FDA Approval to Market a New Drug<sup>4</sup>**

21 CFR 314 applies to studies described in a New Drug Application (NDA). 21 CFR 314 defines the following terms:

**Adverse drug experience.** Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

**Life-threatening adverse drug experience.** Any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

**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 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. **Disability.** A substantial disruption of a person's ability to conduct normal life functions.

**Unexpected adverse drug experience.** Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

## 21 CFR 312 vs. 21 CFR 314

These two regulations define different adverse event terms, as shown in Table 1:

**Table 1. 21 CFR 312 and 21 CFR 314 Adverse Event Terms**

<b>Term</b>	<b>21 CFR 312</b>	<b>21 CFR 314</b>
Adverse event	✓	
Adverse drug experience		✓
Life-threatening adverse event	✓	
Life-threatening adverse drug experience		✓
Life-threatening suspected adverse reaction	✓	
Serious adverse event	✓	
Serious adverse drug experience		✓
Serious suspected adverse reaction	✓	
Suspected adverse reaction	✓	
Unexpected adverse event	✓	
Unexpected adverse drug experience		✓
Unexpected suspected adverse reaction	✓	

Both 21 CFR 312 and 21 CFR 314 apply to many industry-sponsored and other studies.

Although the wording of 21 CFR 312 and 21 CFR 314 terms vary, the core concepts of similar terms are the same, e.g.:

**Serious adverse event.** An adverse event...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... (21 CFR 312)

**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 existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect... (21 CFR 314)

Nevertheless, there are differences in the definitions, and 21 CFR 312 includes definitions without counterparts in 21 CF 314, so it is probably wise to review both sets of definitions when a situation is unclear.

### **21 CFR 310. New Drugs<sup>5</sup>**

21 CFR 310 covers clinical studies of FDA-approved drugs used in unapproved ways, e.g., in a new dosage, formulation, method of administration, or therapeutic area. 21 CFR 310 definitions for adverse event terms are identical to those in 21 CFR 314 above.

### **ICH Guidances**

Three International Conference on Harmonisation (ICH) guidelines define adverse event terms in connection with clinical studies of drugs:

### **ICH Guideline for Good Clinical Practice E6(R1)<sup>6</sup>**

This guideline defines the following terms:

**Adverse Event.** 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 adverse event (AE) can therefore be any unfavourable 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 (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

**Serious Adverse Event or Serious Adverse Drug Reaction.** Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

**Adverse Drug Reaction.** 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.

**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).

FDA's Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance is adapted from this ICH Guideline.<sup>7</sup>

### **ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A)**<sup>8</sup>

This guideline defines the following terms:

**Adverse Event (or Adverse Experience).** 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 unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Adverse Drug Reaction.** 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 products" 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 well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:

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 disease or for modification of physiological function.

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

**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 medicinal product).

**Serious Adverse Event or Adverse Drug Reaction.** During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes

in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: 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.

- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

FDA's Office of Training and Communications, Division of Drug Information includes this guideline in its list of guidance documents for the Center for Drug Evaluation and Research (CDER).<sup>9</sup>

## **ICH Statistical Principles for Clinical Trials (E9)<sup>10</sup>**

This guideline defines a **treatment-emergent [adverse] event** as “an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.”

### **ICH E6(R1) vs. ICH E2A**

ICH E6(R1) covers the conduct of clinical studies, while ICH E2A covers expedited reporting of safety data. For practical adverse event purposes, this is a distinction without a difference. ICH E6(R1) and ICH E2A define the same adverse event terms, except ICH E2A also defines adverse experience as a synonym of adverse event. In addition, ICH E2A provides more guidance, so it should be reviewed when a situation is unclear.

### **Unanticipated Problems**

Some, but far from all, adverse events are unanticipated problems that require expedited reporting to institutional review boards (IRBs).<sup>11</sup>

The Office for Human Research Protections' (OHRP's) “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” defines three adverse event terms:<sup>12</sup>

In this guidance document, the term **adverse event** in general is used very broadly and includes any event meeting the following definition:

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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

In the context of multicenter clinical trials, adverse events can be characterized as either **internal adverse events** or **external adverse events**. From the perspective of one particular institution engaged in a multicenter clinical trial, internal adverse events are those adverse events experienced by subjects enrolled by the investigator(s) at that institution, whereas external adverse events are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered internal adverse events.

FDA's “Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting Improving Human Subject Protection” specifies “**alarming**” adverse events that should be reported immediately as unanticipated problems:<sup>13</sup>

Investigators are required to report promptly to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is “**alarming**,” the investigation must report the adverse effect immediately (5 312.64(b)).

## U.S. National Cancer Institute Guideline

The National Cancer Institute (NCI) has published "Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP AND CIP) and DCP INDs and IDEs," which provides guidance on reporting adverse events in cancer studies:<sup>14</sup>

**Adverse Event (Adverse Experience).** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can 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 considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). (International Conference on Harmonisation [ICH] E2A, E6).

**Life-Threatening Adverse Event.** Any AE that places the subject, in the view of either the investigator or the sponsor (NCI), at immediate risk of death from the AE as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death (FDA 21 CFR 312.32, ICH E2A).

**Serious Adverse Event.** Any adverse drug event (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 existing hospitalization (for >24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon 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 (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**Unanticipated Adverse Device Event.** 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[s]). UADEs must be reported by the clinical investigator to the sponsor and the reviewing Institutional Review Board (IRB), as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor [NCI] and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)).
- Sponsors [NCI] must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b), 812.150(b)(1)).



NOTE: The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

Common Terminology Criteria for Adverse Events (CTCAE): Is designed as an instrument to be used to document AEs identified through a combination of clinical and laboratory evaluation. CTCAE is NOT a tool to assist with data extraction from source documents without the direct participation and supervision of clinical investigators. AE grading and attribution require documentation by medical personnel who are directly involved in the clinical care of protocol subjects.

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI as follows:

**Grade Description:**

- |   |  |
|---|--|
| 0 | No AE (or within normal limits).   |
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.   |
| 2 | Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).      |
| 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. |
| 4 | Life-threatening consequences; urgent intervention indicated.  |
| 5 | Death related to AE.   |

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE, which is defined in Section 2.1.22 (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**Baseline AEs.** Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as 'Course Zero' using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

**Persistent AE.** A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

**Recurrent AEs.** A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

### **Medical Device Regulations, Guidance and ISO Guideline**

Two parts of the U.S. Code of Federal Regulations define and use adverse event terms in connection with clinical studies of medical devices:

## **21 CFR 812 Investigational Device Exemptions and 21 CFR 814 Premarket Approval of Medical Devices<sup>15,16</sup>**

Both regulations define this term:

**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.

This definition covers injuries to subjects but not other persons like surgeons, who might, for example, be exposed to a viral infection if a surgical glove tears. As in the ISO document discussed below, the term "adverse device effect" is limited to adverse events related to the medical device.

21 CFR 814 also defines these terms:

**Serious, adverse health consequences** means any **significant adverse experience**, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are nonlife-threatening and that are temporary and reasonably reversible.

These regulations do not define related terms, such as "adverse event" and "serious adverse event," that are defined in the regulations for drug studies. However, 21 CFR 812 uses these related terms: "adverse effects," "adverse device effects," "adverse effect on health," and "serious adverse effect on health or safety." 21 CFR 814 uses these related terms: "adverse effects" and "adverse reactions and complications."

## **FDA Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications<sup>17</sup>**

This FDA guidance defines several adverse event terms:

**Device-related serious adverse events.** Those events that may have been or were attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.

**Device-related non-serious adverse events.** Those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse event.

**Procedure-related complications.** Harms to the patient that would not be included under serious or non-serious adverse events, and that do not directly result from use of the device. For example, anesthetic-related complications associated with the implantation of a device. Similarly, FDA would factor risks associated with the collection of human biological materials into the benefit-risk determination.

- Probability of a harmful event – the proportion of the intended population that would be expected to experience a harmful event. FDA would factor whether an event occurs once or repeatedly into the measurement of probability.
- Duration of harmful events (i.e., how long the adverse consequences last) – some devices can cause temporary, minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent,

debilitating injury. FDA would consider the severity of the harm along with its duration.

- Risk from false-positive or false-negative results for diagnostics – if a diagnostic device gives a false-positive result, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. If a diagnostic device gives a false-negative result, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition. The risks associated with false-positives and false-negatives can be multifold, but are considered by FDA in light of probable risks.

### **ISO 14155 – Clinical Investigation of medical devices for human subjects – Good clinical practice<sup>18,19</sup>**

The International Standards Organization (ISO) has published good clinical practice standards for conducting studies with medical device trials, with a more complete adverse event taxonomy. The definitions generally track those for medications, except (a) injuries caused/not caused by the device are differentiated and (b) injuries to persons other than study subjects are also covered. For example, a technician calibrating a device could receive an electrical shock. Injuries related to the device are termed “adverse device effects.” For example, if implantation causes an injury because the device or its instructions are defective, it is an adverse event and an adverse device effect. However, if the injury is caused by a hospital-acquired infection unrelated to some deficiency in the device, it is just an adverse event. Unlike the ICH guidelines, the FDA has not adopted ISO 14155 as a guidance of its own.

The standard defines the following terms:

**Adverse device effect.** Adverse event related to the use of an investigational medical device. NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

**Adverse event.** Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

**Serious adverse device effect.** Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Serious adverse event.** Adverse event that (a) led to death, (b) led to serious deterioration in the health of the subject, that either resulted in (1) a life-threatening illness or injury, or (2) a permanent impairment of a body structure or a body function, or (3) in-patient or prolonged hospitalization, or (4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (c) led to foetal distress, foetal death or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a pre-

existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

**Unanticipated serious adverse device effect.** Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: **Anticipated serious adverse device effect** (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

The document uses, but does not formally define the term, “anticipated adverse device effects,” which presumably includes both serious and non-serious effects.

The document includes table F.1, which categorizes adverse events and adverse effects:

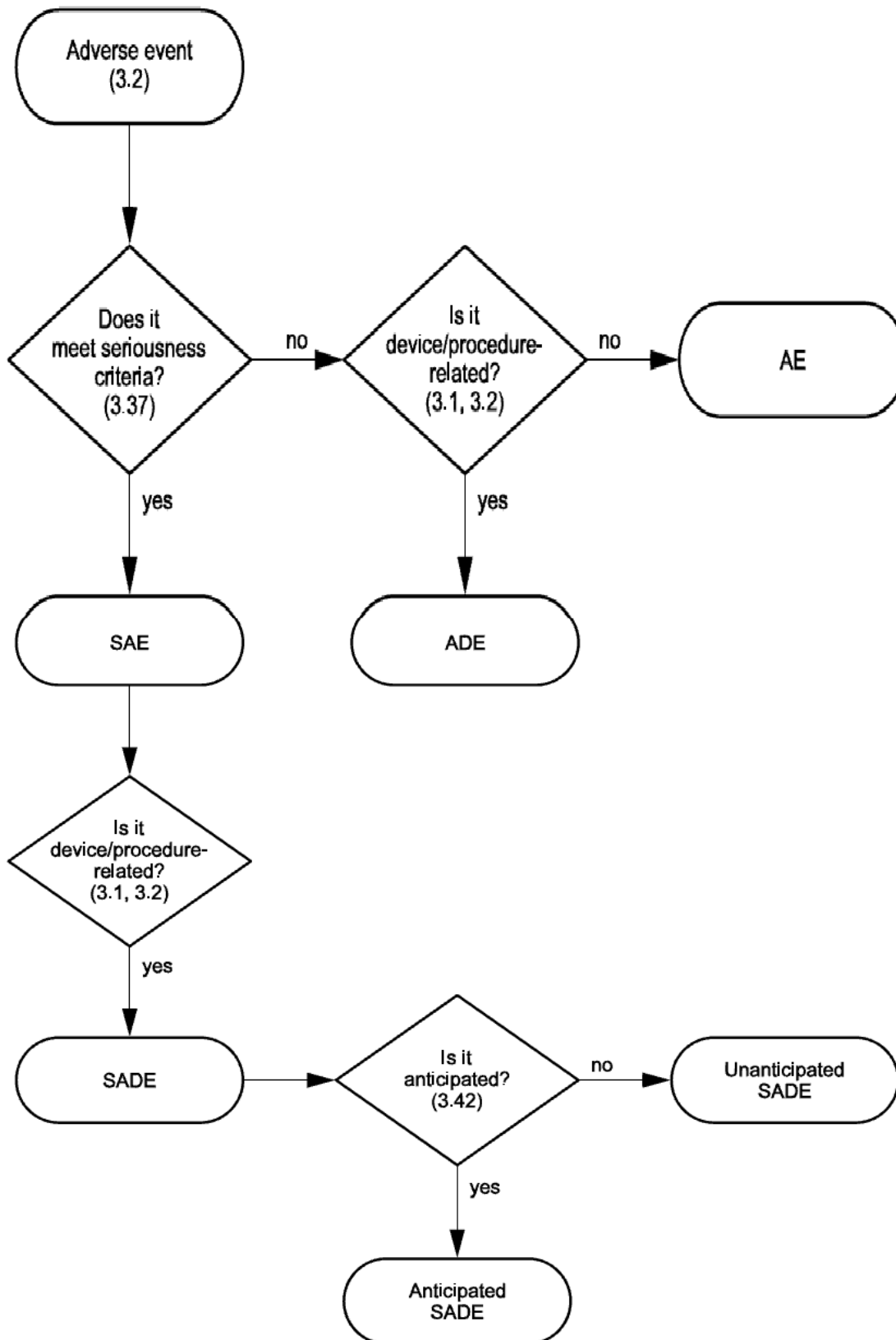
**Table F.1 — Categories of adverse events**

ADVERSE EVENTS	Non-device-related	Device- or procedure-related	
Non-serious	Adverse Event (AE) <sup>a</sup> (3.2)	Adverse Device Effect (ADE) (3.1)	
Serious	Serious Adverse Event (SAE) <sup>b</sup> (3.37)	Serious Adverse Device Effect (SADE) (3.36)	
		Anticipated	Unanticipated
		Anticipated Serious Adverse Device Effect (ASADE) (3.42, Note)	Unanticipated Serious Adverse Device Effect (USADE) (3.42)

<sup>a</sup> Includes all categories.

<sup>b</sup> Includes all categories that are serious.

The standard also includes Flowchart F.2 for categorizing adverse events and effects:



## European Directive and Guidelines

European governing bodies have published three documents that define adverse event terms in connection with clinical studies:

### **European Union Directive 2001/83/EC<sup>20</sup>**

This directive defines the following terms for drug studies:

**Adverse reaction.** A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

**Serious adverse reaction.** An adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

**Unexpected adverse reaction.** An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

### **European Commission Guidelines on Medical Devices: Clinical Evaluation: A Guide for Manufacturers and Notified Bodies (MEDDEV. 2.7.1 Rev.3)<sup>21</sup>**

This guideline defines the following terms for device studies:

**Adverse Event.** Any untoward medical occurrence in a subject. Note: For the purposes of this document, this is intended to include any adverse event whether device related or not.

**Serious Adverse Event.** An adverse event that (1) led to a death; (2) led to a serious deterioration in health of a patient, user, or others that: (a) results in a life threatening illness or injury; (b) results in a permanent impairment of a body structure or body function; (c) requires in patient hospitalisation or prolongation of existing hospitalisation; (d) results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; (e) led to foetal distress, foetal death or a congenital abnormality/ birth defect.

## Other

### **Other Notable Documents**

The following documents might be expected to include definitions of adverse event terms, but do not:

- 45 CFR 46. Protection of Human Subjects does not mention the term "adverse."<sup>22</sup>
- 21 CFR 50. Protection of Human Subjects mentions the term "adverse" only in this sentence:<sup>23</sup>

DOD will provide adequate follow up to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

- 21 CFR 56. Institutional Review Boards does not mention the term "adverse."<sup>24</sup>

- FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (Draft) repeats the definitions in 21 CFR 312.<sup>25</sup>
- ICH E2B(R) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports relies on E2A for adverse event term definitions.<sup>26</sup>
- FDA Guidance: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations (Draft)<sup>27</sup> and European Commission ENTR/CT 4 Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module) discuss but do not define serious unexpected suspected adverse reaction (SUSAR).<sup>28</sup>

## Synonyms

Synonyms of adverse “event” include:

- Effect
- Experience
- Health consequence
- Occurrence
- Outcome
- Reaction (to a drug)

## Other Adverse Event Terms

Other clinical study adverse event terms include the following:

- Adverse reaction profile (21 CFR 315 Diagnostic Radiopharmaceuticals)
- Clinical adverse event (21 CFR 315 Diagnostic Radiopharmaceuticals)
- Significant adverse event (ICH E3 Guideline: Clinical Study Reports)

In pharmacokinetic studies, the following terms are drug toxicity measures:

- Lowest observed adverse effect level (Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers)
- No observed adverse effect level (Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers)

## Acronyms

Although acronyms are largely omitted from the text above, they are commonly used to denote different types of adverse events.

## Conclusion

Clinical researchers who work on international, NIH-funded, industry-sponsored oncology studies involving the use of hybrid drug/device treatments must contend with a dense thicket of adverse event terminologies. Everyone else should count themselves lucky.

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## **Author**

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information services. Contact him at 1.650.465.0119 or [ngoldfarb@firstclinical.com](mailto:ngoldfarb@firstclinical.com).