

# ICTDR Investigator Manual

## MONITORING AND REPORTING ADVERSE EVENTS

INTERNATIONAL CENTERS FOR TROPICAL DISEASE RESEARCH NETWORK  
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES  
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES  
NATIONAL INSTITUTES OF HEALTH

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# Section I: Overview And Introduction

## **Purpose of this Adverse Event Manual**

Each investigator in a research study is responsible for ensuring:

- Safety of subjects.
- Reporting of Adverse Events (AEs).

This manual is designed to serve as a practical teaching tool and resource for investigators and study staff to fulfill these responsibilities.

### **A. It provides basic information for recognizing, collecting, classifying, and reporting AEs.**

The manual contains regulatory information, National Institutes of Allergy and Infectious Diseases (NIAID)/ Division of Microbiology and Infectious Disease (DMID) procedural guidance, and learning exercises to provide investigators and staff with immediate applicable instruction for dealing with AEs.

### **B. The manual is also intended as a resource to help with AE management and study documentation (Protocol and Standard Operating Procedures development).**

It helps ensure that investigators and site staff plan so that when AEs occur, they are handled in a consistent, correct and timely way.

## Organization of this AE Manual

This manual has been organized into the following sections, each addressing a different aspect of AE management:

- Section I: Overview and Introduction
- Section II: Definitions and Concepts
- Section III: Recognizing and Reporting
- Section IV: Building AE Reporting Systems  
- SOP Development
- Section V: Protocol Development
- Section VI: Investigator and Sponsor Responsibilities
- Section VII: Exercises
- Section VIII: Appendices

Each of these sections can be used as an independent module. Together, they should provide a comprehensive summary for Investigators and site staff to build a system for appropriately recognizing, classifying, recording, and reporting of AEs.

## Overview and Introduction

AEs, no matter how clinically insignificant, should **never** be ignored; they may indicate onset of more clinically significant pathology.

Systematic monitoring and reporting of AEs that occur during a study is necessary to alert the clinical investigators, the study sponsors, and others of real and potential patient safety issues arising during the course of the study.

**Section I** provides the significance of AE reporting and the background for use of this manual.

## Definitions and Concepts

For accurate identification and management of AEs, using common terminology is essential.

Investigators and designated staff need to be able to distinguish between:

- Expected vs. unexpected AEs.
- Serious vs. non-serious AEs.
- Possible relationships of AEs to study drug (products) or procedures.
- Severity grading vs. seriousness of AEs.

**Section II** provides the most important definitions and terms for use in developing AE management strategies and reporting systems.



## Recognizing and Reporting

Some subjects experience AEs, unwanted effects on the body, in most clinical research studies. Investigators or designated study team members are responsible for appropriately recognizing, classifying, recording, and reporting these AEs.

The purpose of AE reporting is:

- To monitor and assure the safety of study subjects.
- To capture safety-related data in a systematic fashion.
- To contribute to the safety profile of the product.
- For investigational agents:  
To contribute to early toxicity profile, alert regulatory agency, sponsor, and investigators of potentially serious safety issues, and contribute to labeling information.

**Section III** outlines how to recognize AEs and how to correctly document and report them.

## **Building AE Reporting Systems - SOP Development**

Standard Operating Procedures (SOPs) are “detailed, written instructions to achieve uniformity of the performance of a specific function.” (ICH Guidelines E6 1.5.5)

They should describe how to carry out specific activities relevant to conduct of a research study.

Standardized AE reporting facilitates the accumulation of new and important safety information. Improved reporting of AEs leads to improved subject safety and may ultimately lead to improved product safety profiles.

**Section IV** is designed to provide investigators and sites with tools for effective development and standardization of AE reporting systems within the framework of their SOPs.

## Protocol Development

A well-designed protocol is the prerequisite for a successful research study.

The study protocol provides the background and rationale for a research study, describes the study design, and explains what will happen and what procedures will be followed during the course of the study.

A well-written clinical protocol addresses the following issues:

- Careful identification of possible AEs.
- Description of procedures for monitoring the occurrence of AEs.
- Provision of appropriate medical and toxicity management to subjects experiencing the AEs.
- Standardized AE reporting procedures.

**Section V** provides guidelines for incorporation of AE and Toxicity Management into the study protocol.

## Investigator and Sponsor Responsibilities

In all clinical research involving human subjects, there is a set of pre-determined responsibilities for the investigator and the sponsor to ensure that the two main principles of GCP are being followed:

- Protection of human subjects.
- Collection of clean and reproducible data.

Identification and management of AEs during the course of a study serves both goals. The Investigator and sponsor obligations to protect the safety of study subjects are defined in the Code of Federal Regulations (CFR) for U.S. research and in the International Conference for Harmonisation (ICH) guidelines.

**Section VI** lists and explains the main responsibilities of the sponsor, investigator, and site regarding AE reporting obligations.

## Exercises

**Section VII** provides exercises for investigators and site staff. They are intended to illustrate the principles laid out in this manual for monitoring and reporting adverse events.

## Appendices

**Section VIII** contains relevant resources and documents regarding AE reporting obligations for the investigators and site staff.

# Section II: Definitions And Concepts

## AE Definitions

AEs are broadly defined as **ANY** untoward deviations from baseline health which include:

- Worsening of conditions present at the onset of the study.
- Subject deterioration due to the primary disease.
- Intercurrent illness.
- Events related or possibly related to concomitant medications.

These can include “unwanted effects”:

- Symptoms (e.g., headache, nausea, dizziness).
- Physical findings (e.g., elevated BP, hair loss, hepatosplenomegaly).
- Syndrome of disease.
- Abnormal lab values.
- Overdose.
- Toxicities.

ICH defines an AE as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH Guidelines E2A)

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding).
- Symptom or disease, temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.



AEs are not limited to **DRUG** side effects!  
**ANY** medical change from baseline is an AE.

Baseline is the protocol designated timepoint from which changes in status are measured.

The time point established as the participant's baseline when AE reporting begins depends upon the study design, but will be the same for all participants enrolled in the study.

Common starting points for AE reporting are:

- After a subject has provided **Informed consent**
- After a subject has been **randomized**
- After a subject has **received the intervention** for the first time

## Grading the Severity of AEs

### *Estimating Severity Grade*

All AEs will be assessed by the investigator using the protocol defined grading system.

The use of a standard table for interpreting and grading abnormal signs, symptoms and laboratory parameters is recommended.

If the protocol has no defined grading system, or if the AE is not described in the existing grading system, the following guidelines should be used to qualify severity:

**Grade 1: Mild** -Transient or mild discomfort (<48 hours); no medical intervention/ therapy required.

**Grade 2: Moderate** - Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/ therapy required.

**Grade 3: Severe** - Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

**Grade 4: Life Threatening** - Extreme limitation in activity; significant assistance required; significant medical intervention/ therapy required, hospitalization or hospice care probable.

## **“Expected” vs. “Unexpected” AEs**

### ***“Expected” AEs:***

Any AE whose nature and severity have been previously observed and documented for the study product.

Generally speaking, expected AEs are identified in the Investigator's Brochure or the package insert for the product.

### ***“Unexpected” AEs:***

ICH defines this as any AE, the nature or severity of which is not consistent with the applicable product information.

A broader definition would include any AE that has not been previously observed (i.e., included in the labeling or investigator's brochure), whether or not the event is anticipated because of the pharmacologic properties of the study agent.  
(ICH Guidelines E2A)

## **Serious Adverse Event Definition**

Serious Adverse Events (SAEs) are defined as follows:

- **Death** during the period of protocol defined surveillance;
- **Life-threatening** (defined as a subject at immediate risk of death at the time of the event);
- Resulting in **hospital admission** during the period of protocol defined surveillance, or prolongation of existing hospitalization;
- Resulting in a persistent or significant **disability/ incapacity**;
- Resulting in **congenital anomaly** or **birth defect**;
- Any **other important medical event** that may not result in death, be life threatening, or require hospitalization, when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

### ***DON'T Confuse Seriousness With Severity!***

**Serious** is a regulatory definition.

**Severity** refers to an intensity classification  
(mild, moderate, severe)

## AE Relationship to Study Product

The possible relationship of an AE to use of study product is assessed by the Investigator. The terminology for these assessments can vary from one reporting system to the next.

The DMID (S)AE reporting system uses the following terms to describe the relationship of an AE to the study product:

- |  |  |
|--|--|
|  | <ul style="list-style-type: none"><li>▪ <b>Definitely</b> Clear-cut temporal association, and no other possible cause.</li><li>▪ <b>Probably</b> Clear-cut temporal association, and a potential alternative etiology is not apparent.</li><li>▪ <b>Possibly</b> Less clear temporal association; other etiologies also possible.<br/><br/>Temporal association between the AE and the study product and the nature of the event is such that the study product is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).</li><li>▪ <b>None</b> The AE is completely independent of study product administration; and/or evidence exists that the event is definitely related to another etiology.</li></ul> |
|--|--|

## Section III: Recognizing And Reporting

## Introduction

In most clinical research studies, some subjects can experience AEs that are unwanted effects on the body. As the investigator or his/her designee, you are responsible for appropriately recognizing, classifying, recording, and reporting these AEs.

The purpose of AE reporting can be summarized as follows:

- To monitor and assure the safety of study subjects.
- To capture safety-related data in a systematic fashion.
- To contribute to the safety profile of the product.
- For investigational agents:  
To contribute to early toxicity profile, alert regulatory agency, sponsor and investigators of potentially serious safety issues, and contribute to labeling information.

## Overview of DMID Requirements for AE Reporting

AE reporting is an essential component of any research involving human subjects. DMID requires notification of the occurrence of **all** AEs.

The purpose of this guidance is to provide a consistent structure for AE reporting on DMID sponsored trials.

Many investigators are aware that AE reporting requirements apply only to intervention studies. It is important for investigators to be familiar with the broad definition for “intervention” according to US Code of Federal regulations 45CFR46.102.

**Excerpt from  
45CFR46.102:**

**Definition of  
Intervention:**

**“Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.”**

The AE reporting system should be described in the protocol for implementation at the study's initiation. The system must include:

- Adopted definition of AE.
- Standard table used for interpreting toxicity and grade of AE.
- Standardized form used for reporting AE.
- Description of how AEs will be captured.
- Assignment of study personnel responsible for recording AE.
- System for processing and forwarding AEs to IRB, DMID and/or other sponsor.

The DMID has adopted standard toxicity tables for grading AEs (attached as Appendices in Section VIII). However, other standardized toxicity tables (for instance, WHO, NCI, DAIDS), may be applied to protocols if found to be more suitable.



## **Overview of DMID Requirements for AE Reporting (cont.)**

DMID clinical research studies involve many different diseases and populations. Studies supported by the DMID involve a wide range of diseases (mild to severe), populations (children, elderly, immuno-compromised, poor nutritional status) and study products (Phase I to post-marketing studies of well characterized agents).

Protocol design is expected to reasonably accommodate these differences to prevent unduly burdensome reporting. For example, the definition of anemia requiring reporting can be adjusted in studies investigating malaria so that those patients observed to have a change in baseline value over that expected in the general population will be captured. However, this adjustment must be made by a reasoned justification in the protocol, based on scientific evidence that is disease and/or population specific.

AEs including local and systematic reactions not meeting the criteria for “SAEs” (serious adverse events) should be captured on the appropriate case report form. These events should be followed to resolution.

A sample AE form is located in Section VIII.

## Timeframe for SAE Reporting

SAE reporting must adhere to the following time frame:

A written report of the following events (on standard DMID SAE form; available in Section VIII) must be sent to the SAE office, DMID Program Officer or to the assigned contact as designated for the study within the stated timeframes:

- Fatal or Life Threatening events with any possible association with use of study product or participation in the study must be reported within **24 hours** after the site's awareness of the event.
- Other AEs that are both Serious and Unexpected with any possible association with the use of the study product or study participation must be reported within **3 calendar days** after the site's awareness of the event.

SAE reports are sent to DMID by one of 3 routes:

- Via designated safety FAX (**+1-301-435-3649**).
- To the Medical Officer or Program Officer.
- Through the DMID on-line AE reporting system (this route requires advance protocol registration).

The route is determined prior to protocol implementation and is consistent for all SAE reports for a given study.

### **REMEMBER.....**

**In determining whether an AE is serious and should be reported to DMID, you must consider:**

- **Toxicity grade**
- **Relationship to study agent**
- **Timeframe during which the event occurred**
- **If the event meets protocol specific reporting criteria**

**If in doubt, submit the AE report to DMID!**

## **AEs that Are Reportable to the FDA (Unexpected and Serious)**

For studies using investigational agents, there are absolute minimal requirements for SAE reporting from the site to the sponsor, to ensure that the sponsor can meet FDA requirements.

It is the investigators responsibility that **any AE** that is both serious and unexpected, be reported to the sponsor as soon as the site becomes aware of the event.

Deviations from these standard requirements occur, however, they **must** be agreed to by all parties (investigator, sponsor and FDA if applicable) and predefined in the protocol:

### ***Examples***

- Diagnoses, illnesses or lab abnormalities assessed by the investigator to be 'not related' to study treatment and with the alternative, definite etiology documented in the participant's medical record.
- Participant experiences a recurrent episode of a previously reported AE that is at the same level as experienced previously (that is, the condition is not worsening).

## **Expedited vs. Routine (Periodic) Reporting**

### ***Expedited Reporting***

SAEs are usually subject to Expedited Reporting. Regulatory authorities (e.g. FDA) require that sponsors report the occurrence of SAEs to them within specific timeframes to ensure early and prompt identification of serious potential risks associated with the agent. To ensure compliance with these guidelines, investigators are required to initiate the reporting process for SAEs, often before complete information about the event is available.

### ***Periodic Reporting***

In addition to expedited reporting, investigators and sponsors are often required to prepare periodic reports of AEs. These reports identify AEs that occur during a specific period.

AEs that are expected and those graded as mild or moderate are not reported in an expedited fashion. Unlike expedited reporting, the occurrence of any one of these events is unlikely to demonstrate a change in risk or result in immediate changes in the risk/benefit assessment.

The content and structure of periodic reports depends upon the study. These reports may include all AEs reported during the period or a subset .

Examples are:

1. All AEs that are grade 3 and higher,
  2. All AEs that were judged to be probably, possibly or definitely related to study therapy, or
  3. All AEs related to a specific organ system, etc.).
- The content, structure and frequency of periodic reports should be described in the protocol in the study monitoring plan.

### ***The Value of Periodic Reporting:***

The value of Periodic Reporting lies in:

- Assessing trends in the accumulating/cumulative data;
- Assessing frequency of lower grade AEs in the study population;
- Detecting revealing differences in treatments;
- Assessing tolerability of agents.

### ***Formats for Periodic Reports***

Formats for periodic reports may include:

1. LINE LISTINGS (summary of information for each AE);
2. FREQUENCY TABLES (organized by Body Systems);
3. NARRATIVE ACCOUNTS (descriptions of events).

## Follow Up Reports

The investigator must submit follow-up SAE information to the sponsor if one of the following applies:

- Change in relationship assessment of toxicity grade;
- Change in the etiology or clarification of the primary SAE;
- Requested by the sponsor.

Upon request of the sponsor, investigators are required to submit additional information as soon as possible. Additional information may include an updated SAE form, copies of diagnostic test results, laboratory reports or medical notes. Copies of clinical notes and records should not include the subject's name, but should include study number and study numbers assigned.

For SAEs that become FDA Safety Reports, the SAE Office may need to contact the site in the immediate period after reporting for important follow-up information.

**If an FDA safety report is required,  
DMID - as the sponsor of the research -  
has to file that report with the FDA  
within 7 or 15 days of receipt of the SAE  
(depending on the nature of the SAE).**

### ***DON'T Confuse Seriousness With Severity!***

**Serious** is a regulatory definition.

**Severity** refers to an intensity classification  
(mild, moderate, severe)

## Report to the Institutional Review Board(s)

Investigators are reminded that the IRB at each participating institutions has a responsibility to develop procedures for the review of AEs occurring during the study. At a minimum, IRBs need to receive copies of all expedited safety reports.

***Investigators need to familiarize themselves with and adhere to the IRB's requirements for reporting AEs.***

## Interactions with Independent Monitors

All clinical studies require ongoing data and safety monitoring. The method and intensity of independent safety monitoring should be based on the degree of risk involved, the size, and complexity of the study. The sponsor (DMID) is always responsible for safety monitoring of a clinical study.

Additional independent safety monitoring can be performed by an Independent Study Monitor, Safety Monitoring Committee, or a Data and Safety Monitoring Board (DSMB). These individuals and groups need to be kept informed of AEs occurring during a research study.

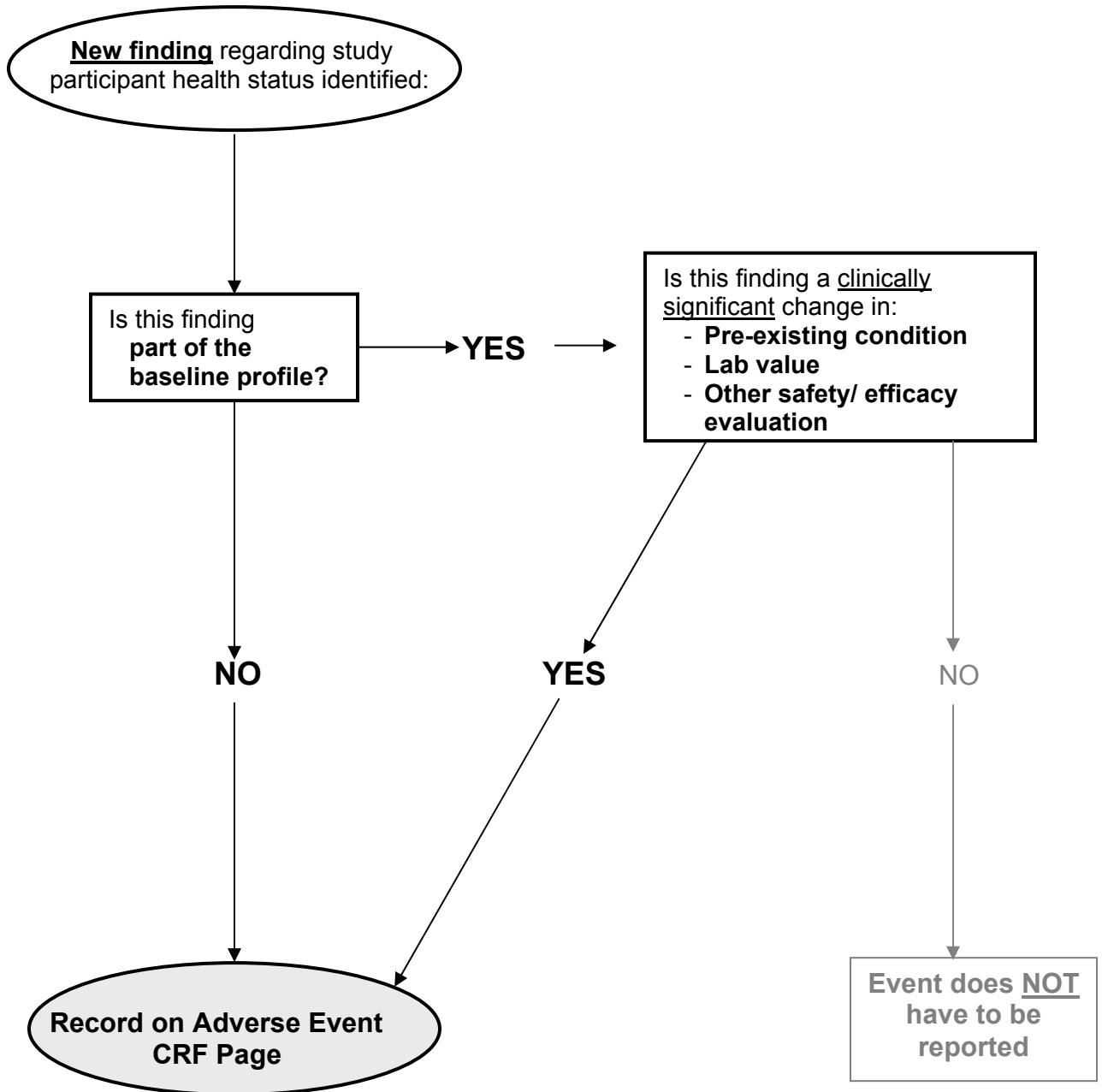
- Independent safety monitors have special responsibility to review study data with the safety of the participants as the foremost concern.
- The investigator has an obligation to provide data in as timely, accurate, and complete form as possible.
- Independent safety monitors may be seeing grouped/blinded data and identify additional safety concerns.
- Independent safety monitors may request additional information from the site and/or investigator.

- Independent study monitors often request additional follow-up information.
- Collection of additional information may necessitate protocol amendments.



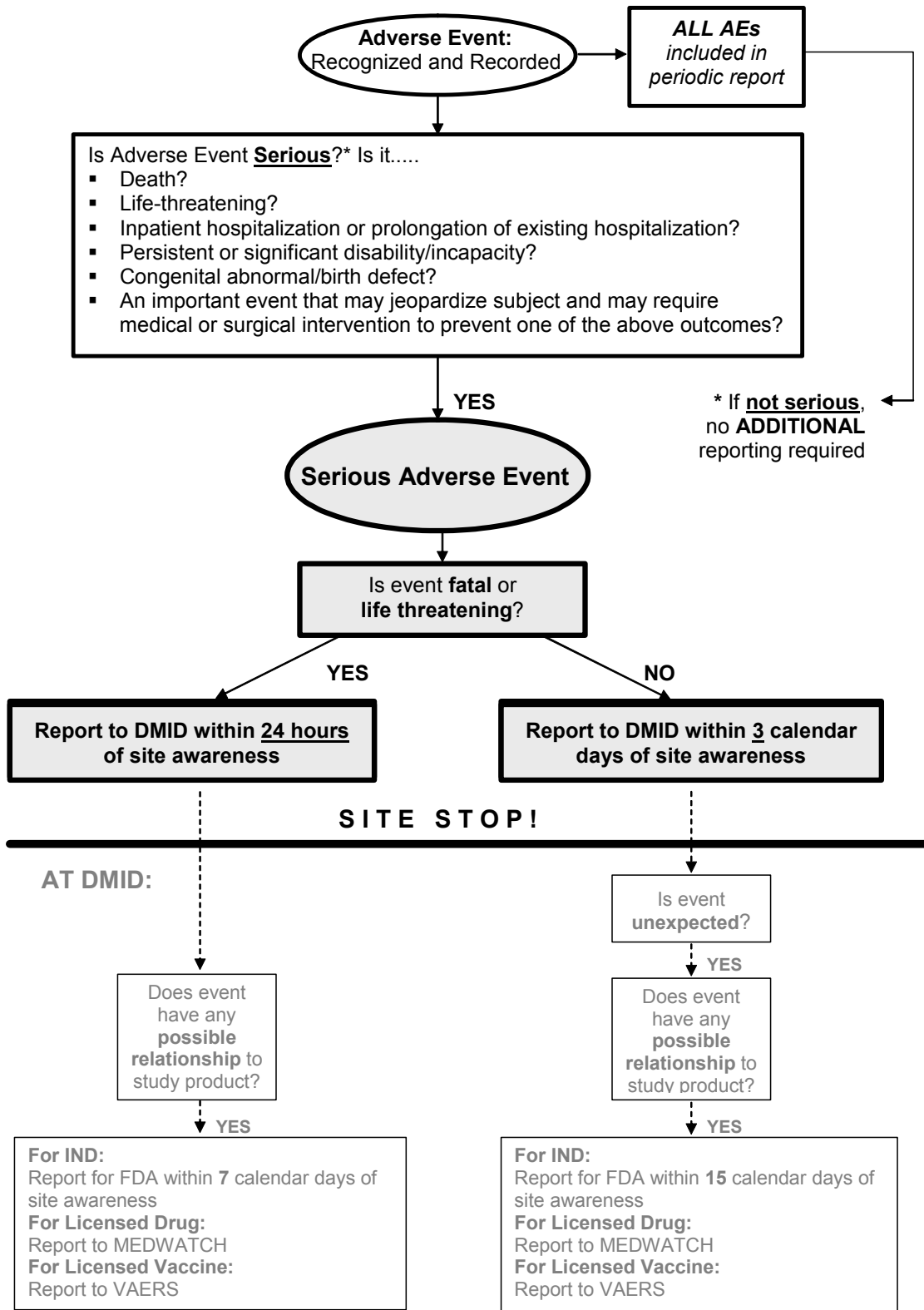
## AE Decision Flow Chart

AT THE SITE:



# SAE Reporting Flowchart

AT THE SITE:



## Section IV:

# Building AE Reporting Systems - SOP Development

## Introduction

Standard Operating Procedures (SOPs) are “detailed, written instructions to achieve uniformity of the performance of a specific function.” (ICH Guidelines E6 1.5.5)

They should describe how to carry out specific activities relevant to conduct of a research study.

Standardized AE reporting facilitates the accumulation of new and important safety information. Improved reporting of AEs leads to improved subject safety and will ultimately lead to improved product safety profiles.

## Writing Standard Operating Procedures (SOPs)

The purpose of SOPs is to provide detailed instructions to site staff for conducting any study activities in a standardized fashion.

They address the basic “WHO? WHAT? WHEN? WHERE? HOW?” of a study, whereas the “WHY” should be explained in the protocol.

SOPs should be written in such a way that any trained staff can carry out a specified activity by following a given set of instructions.

The format of your SOPs should include:

- Purpose.
- Effective Date.
- Who the SOP applies to.

The contents of the SOPs should include

- Which procedures are to be done.
- Who is qualified to carry out a specific procedure.
- How these study procedures are to be carried out.
- How deviations from standard procedures will be handled.

SOPs have to be maintained and updated throughout the life of a study. They become part of the essential study documents. They form an important part of new staff training materials.

## Developing Operating Procedures (SOPs) for Recognizing and Reporting AEs

The purpose of SOPs for AE recognition and reporting is to ensure accurate, timely and complete identification of AEs associated with the study by:

- **Clearly defining roles and responsibilities** for all aspects of the identification and reporting of AEs.
- **Expedient recognition** of AEs after they have occurred.
- **Defining a consistent approach** for team members when investigating, managing, recording and reporting AEs.

The team should be familiar with ICH E6 section 4 (Investigator) when drafting their SOPs.

## Ongoing Assessment and Quality Assurance for Safety

1. Develop Study Policy and Procedures for:
  - Routine assessment for potential AEs
    - Routine Reporting of AEs
      - Reporting of SAEs
        - Expedited Reporting of SAEs
2. Policies and Procedures need to:
  - Identify the roles and responsibilities of study team members:
    - Who is responsible for evaluating AEs?
    - Who is responsible for monitoring subjects with AEs?
    - Who determines changes in treatment/dose modifications?
    - Who completes AE reports?
    - Who submits the AE reports?
  - Determine the frequency and procedures for AE review systems:
    - How will data needed for evaluating AEs be provided to the investigator or lead protocol physician?

## Delegation of Responsibilities for AE Reporting at the Sites

Responsibilities for AE assessment and follow-up should be allocated among team members based on the specific characteristics of the study, team members' qualifications, severity of AEs, patient population, performance sites, etc.

- **Team members:**  
e.g., field team members visiting subjects in their expected homes are likely to require closer supervision than physicians and experienced registered nurses.
- **Performance sites:**  
e.g., Field studies in remote locations require different procedures than studies conducted in hospital-based studies. for the recognition and management of severe AEs, as well as the reporting and follow-up.

**Note:**

**The Principal Investigator of the study can delegate responsibilities to qualified members of the study team, but this does not mean that he/she abdicates these responsibilities.**

**The Principal Investigator is always fully accountable for everything that occurs (or doesn't occur) during the study.**



## Worksheet to Develop Procedures for AE Monitoring and Reporting

ACTIVITY	HOW	WHO Field Worker, Study Coordinator, Physician, Data Manager, Investigator	WHEN i.e. scheduled visit/ unscheduled visit/ follow-up visit/ within x hours or weeks	WHERE i.e. field, clinic/ hospital, data center
<b>A. Initial Identification of potential AEs</b> Occurs in at least 3 ways: 1. routine study visit 2. patient initiated study visit 3. brought to team attention after the event is over (i.e. treated at non-study clinic, ER, etc.)	Query each subject at each contact (scheduled or unscheduled visit) about potential AEs. – this information should be collected and reported in an organized form			
<b>B. Review of data by physicians (or Sr. personnel)</b> Check completeness of recorded data, appropriate terminology, accuracy of grading.				
<b>C. Management of AEs</b> 1. Determine need for additional tests 2. Treatment 3. Follow-Up				
<b>D. Determine type of reporting required</b> <ul style="list-style-type: none"> <li>▪ SAE</li> <li>▪ Non-serious AE</li> </ul>				
<b>E. Complete AE Forms</b> Who completes? Who reviews? Who signs?				
<b>F. Submit Serious SAE forms</b>				
<b>G. Respond to Sponsor Queries</b>				
<b>H. Follow-Up of AEs</b>				
<b>I. Informing IRB(s)/ DSMB</b>				
<b>J. Quality Assurance Procedures for AEs</b>	e.g. create and maintain an AE log and use chart review to determine if all AEs recognized, all SAEs reported to sponsor, IRB, all AEs followed until resolution, etc.			

# Section V: Protocol Development

## Good Clinical Protocol Design

The study protocol provides the background and rationale for the research study, describes the study design, and explains what will happen/ which procedures will be done during the course of the study.

A well designed protocol is the prerequisite for a successful research study.

Good clinical protocol design requires:

- Careful identification of likely AEs.
- Description of procedures to monitor for the occurrence of AEs.
- Provision of appropriate medical management to subjects experiencing the AEs.
- Standardized AE reporting procedures.

## **Building Safety into Study Design and Protocol Development**

All components of the AE reporting system should be described in **the protocol** prior to implementation, including:

- Clear definition of AEs appropriate to the specific study.
- Standard table to interpret toxicity and grade of AE.
- Standardized form to report AEs.
- Description of how AEs will be recognized and reported.
- Assignment of study personnel responsible for recording AEs.
- System for processing and forwarding AEs to IRB, DMID and/or other sponsor.

***For research studies, where the site already has existing SOPs for AE management - e.g. if participating in network studies, which follow network-wide requirements - these SOPs can be appended to the protocol.***

## Ensuring Adequate Data Capture

Investigators should ensure that all safety data is being appropriately recorded in source documents according to sponsor specifications (see Section VIII “DMID Source Documentation Guidelines (Revised March 11, 2002”).

Capture of safety information in the Case Report Forms is essential. Some information related to AEs will be on standard forms completed at scheduled visits (see sample form in Section VIII). Other data may only be collected on event-driven forms when necessary.

When designing data collection forms, the investigator needs to ensure that there is a place on the forms to capture all necessary information.

Examples include:

- Presence or absence of abnormal signs or symptoms.
- If abnormal signs or symptoms are present, the toxicity grades of those parameters.
- Start/Stop dates of abnormal signs or symptoms.
- Changes (including discontinuation) in dosages of study medications and reasons and dates.
- Initiation of or changes (including discontinuation) in concomitant medications and dates.

## Grading the Severity of AEs

### *Estimating Severity Grade*

All AEs will be assessed by the investigator using the protocol defined grading system.

The use of a standard table for interpreting and grading abnormal signs, symptoms and laboratory parameters is recommended. DMID has adapted a version of a standard toxicity table for pediatric and adult populations. The DMID toxicity table for grading AEs is organized by body systems and includes 4 grades for each represented parameter [see Appendix in Section VIII].

If the protocol has no defined grading system, the following guidelines will be used to qualify severity:

**Grade 1: Mild** - Transient or mild discomfort (<48 hours); no medical intervention/ therapy required.

**Grade 2: Moderate** - Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/ therapy required.

**Grade 3: Severe** - Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

**Grade 4: Life Threatening** - Extreme limitation in activity; significant assistance required; significant medical intervention/ therapy required, hospitalization or hospice care probable.

This grading scheme is generally in concert with other commonly used scales such as the WHO table, NCI Common Toxicity Criteria, and DAIDS Toxicity Table. Explicit in several of these and implicit in the DMID toxicity table is that a Grade 5 toxicity is a fatal AE.

## Grading the Severity of AEs (cont.)

The selection of the standard table for grading abnormal signs, symptoms, and laboratory parameters must be made **prior** to study implementation and adhered to throughout the study by all clinical sites.

### ***Developing New Criteria and Modifying Existing Criteria:***

Standard toxicity tables, including the DMID Toxicity Table, are designed to include most commonly applicable parameters. However, they may not include ALL parameters you may wish to monitor for a given study. In addition, values in the table may not be appropriate for a given study. Reasons for this include:

- Many laboratory parameters are graded as deviations from the laboratory normal values [often expressed in reference to the Upper Limit of Normal (ULN) or Lower Limit of Normal (LLN)]. They may need to be adapted for field and other laboratories that have not established normal values.
- The study population may differ substantially from “normal” at baseline.
- The standard toxicity table may not include parameters or symptoms that should be assessed in your study.

Study-specific parameters to be monitored can be developed for and included in each protocol.

The guidelines for estimating severity grades for abnormalities not included in the Toxicity Table listed above are copied from the first page of the DMID Toxicity Table. While primarily designed to guide the reporting of unusual individual AEs as they occur, these guidelines are also useful for modifying criteria or developing grading criteria for anticipated abnormalities not present in the current Toxicity Table.

## Grading the Severity of AEs (cont.)

### *Incorporating New Criteria into the Protocol Document:*

Investigators and protocol teams should **not** make any changes in grading or additions directly to the DMID Toxicity Table or any other standardized grading scheme.

(The practice of modifying existing tables leads to errors. It is difficult to ensure that one is using the original toxicity table if there are many versions in circulation.) Instead, these modifications should be described in the protocol document in the AE reporting section (see examples below).



## Grading the Severity of AEs – Examples

### *Example 1: Including protocol specific grading in protocol document*

<p><b>SECTION 6.3: TOXICITY MANAGEMENT AND GRADING:</b></p> <p><u><i>Protocol-Specific Grading for Local Reactions</i></u></p> <p>The area of the reaction is calculated by the product of the largest diameter of the induration and its perpendicular (roughly proportional to the area of induration).</p> <p>Local reactions will be graded as follows:</p> <p><b>Grade 1:</b> Erythema, edema or induration &lt;25 cm<sup>2</sup></p> <p><b>Grade 2:</b> Erythema, edema or induration 25-100 cm<sup>2</sup></p> <p><b>Grade 3:</b> Erythema, edema or induration &gt;100 cm<sup>2</sup>, ulceration, phlebitis or superinfection</p> <p><b>Grade 4:</b> Necrosis</p>
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### *Example 2: Excerpt from a protocol-specific toxicity table*

Toxicity / Grade	0	1	2	3	4
LYMPHATICS					
Lymphatics	Normal	Mild lymphedema	Moderate lymphedema pitting	Severe lymphedema Limiting function	Severe lymphedema Limiting function with ulceration
MALE GENITAL EXAM					
New hydrocele	None	Present			
Testicular/ scrotal pain	None	Mild	Moderate	Severe	Disabling

## Developing Appropriate Safety Monitoring Strategies

Identify the clinical signs, symptoms, or laboratory parameters that should be monitored to ensure appropriate recognition of AEs.

For each parameter identified, determine the frequency and duration of monitoring. . The frequency and duration of monitoring should be sufficient to cover the period when AEs are most likely to occur.

For licensed agents, frequency and duration of safety monitoring should be at least equivalent to commonly accepted standards of medical practice.

The team should consider additional safety monitoring when:

- the study dose is different from that usually given.
- the population age range is different.
- the study population may be more susceptible to AEs due to diagnosis of interest, likely intercurrent conditions, or concomitant medications.

Abnormal signs, symptoms or laboratory parameters identified during the study period should be followed by the investigator until the abnormality resolves or stabilizes.

## Identifying Expected AEs for an Intervention

(sometimes known as “listed” AEs)

### ***Source Documents for Expected AEs:***

- For a medicinal product not yet approved for marketing, a company’s Investigator’s Brochure serves as the source document for identifying expected AEs.
- For products that are approved for marketing, expected AEs are those identified in the approved regulatory material. In the United States, this is the Product Package Insert.
- If an Investigator’s Brochure or US Product Package Insert is not available, the protocol must identify the source document that will be used for the study. Options include documents approved by non-US drug regulatory agencies, monographs, and reviews of the agent or compilations of relevant data such as found in MicroMedex or other peer-reviewed clinical information systems. Essential information should be incorporated into the protocol. This source document must be provided to and approved by the sponsor (DMID) in advance. This source document must be maintained on site in the investigator files for the study.

Not included in “expected AEs” are those that might reasonably be anticipated based on the pharmacological properties of the agent (but have yet to be observed and reported). For example, methemoglobinemia would not be considered an expected AE in the evaluation of a new 8-aminoquinolone, even though it is an adverse associated with that class of compounds.

Also not included in “expected AEs” are additional occurrences of a newly recognized AE. These events need to be reported until source documents are amended (new version of an Investigator’s Brochure, change in labeling). For example, elevations in cholesterol and triglycerides associated with combination HIV therapy were subject to expedited reporting until revised Investigator Brochures were available.

## Approach to Safety Management for AEs

In the protocol, the investigator should determine the appropriate clinical management strategy for expected AEs.

The team needs to consider:

- ☞ Laboratory and other procedures necessary to monitor AE.
- ☞ Interruption or discontinuation of study therapy.
- ☞ Supportive therapy or symptom management.
- ☞ Criteria for re-introduction or resumption of original dose of study treatment (or permanent discontinuation).

For studies using more than one study treatment, the dose changes associated with AEs need to be included for each study agent.

Toxicity management sections are often the most complex and confusing sections in a protocol. Clarity in this section is critical and investigators are encouraged to make these sections as understandable as possible through plain language, tables, and other visual aids.

## Approach to Clinical Management for Expected AEs

**Example: dose modification and treatment interruptions based on expected AE (including requirements for more frequent monitoring)**

### **Section 6.3: Toxicity management of ribavirin – Anemia**

#### Dose Reduction of ribavirin

- ☞ The initial starting dose of ribavirin in this study is 600 mg/day with escalation to a maximal dose of 1000 mg/day.
- ☞ There will be no dose reduction to less than 600 mg per day. Subjects may continue with the other drug in their treatment arm if the ribavirin is temporarily discontinued.

#### Additional monitoring for hemoglobin levels:

- ☞ A follow-up hemoglobin measurement must be repeated 2 and 4 weeks after any change of a ribavirin dose (increase or decrease).

**Table:**

*Ribavirin Dose Adjustment for a Decreasing Hemoglobin*

<b>HEMOGLOBIN</b>	<b>RIBAVIRIN DOSE AT THE TIME OF TOXICITY</b>	<b>ACTION</b>
<b>Grade 1</b> 9.5 - 10.5 gm/dL	1000 mg/day	600 mg/day: 200 mg in a.m. and 400 mg in p.m. q 12hrs
	800 mg/day	Temporarily hold drug
	600 mg/day	Temporarily hold drug
<b>Grade 2</b> 8.0 - 9.4gm/dL	All doses	Temporarily hold drug

Section VI:  
Investigator And Sponsor  
Responsibilities

## Introduction

In all clinical research involving human subjects, there is a set of pre-determined responsibilities for the investigator and the sponsor to ensure that the two most important principles of GCP are being followed:

- Protection of human subjects;
- Collection of clean and reproducible, data.

Identification and management of AEs during the course of a study serves both purposes. The investigator and sponsor obligations to protect the safety of study subjects are spelled out in the Code of Federal Regulations (CFR) for U.S. research, and in the International Conference for Harmonisation (ICH) guidelines.

## Responsibilities of Investigators for Safety Assessment and AE Reporting

Investigators performing clinical research sponsored by DMID are responsible for:

- Ensuring a qualified physician who is an investigator or sub-investigator is responsible for all trial-related medical decisions. (ICH Guidelines E6 4.3.1 Investigator)
- Ensuring that adequate medical care is provided to a subject for any AEs, including clinically significant laboratory values, during and following a subject's participation in a trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. (ICH Guidelines E6 4.3.2 Investigator)
- Immediately reporting all serious AEs to the sponsor, except for those SAE's that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. (ICH Guidelines E6 4.11.1 Investigator)
- Reporting AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and with the time periods specified by the sponsor in the protocol. (ICH Guidelines E6 4.11.2 Investigator)
- Supplying the sponsor and the IRB with any additional requested information regarding reported deaths. (ICH Guidelines E6 4.11.3 Investigator)



## **Responsibilities of Sponsors for Safety Assessment and AE Reporting**

### ***The Division of Microbiology and Infectious Diseases (DMID)***

As the sponsor of clinical research, DMID has the responsibility to:

- Review all information relevant to the safety of products administered as a part of supported research.
- Inform concerned investigators and institutions of unexpected SAE related to an investigational product.  
(ICH Guidelines E6 5: Sponsor)
- Review SAE Reports and use this information to monitor the investigational product's toxicity profile and subjects' safety.
- Report AEs that are serious, unexpected, and possibly related to an investigational product to the FDA in the form of a written Safety Report. Safety Report submissions to the FDA must occur as soon as possible, but no later than 7 calendar days if the AE was fatal or life-threatening, otherwise 15 calendar days after DMID is informed about the SAE.  
(21 CFR 312.32 IND Safety Reports)
- Conform to regulatory requirements for submission of safety updates and periodic reports to the FDA.  
(ICH Guidelines E6 5: Sponsor)

# Section VII: Exercises

**Example/ Exercise:**

In the example below,

- the “Current Labeling” column left includes events that are either identified in the **Investigator’s Brochure** or labeled in the **package insert** as being expected;
- the “AE/Patient Presents” column contains events that a patient experienced;
- for each, identify whether the actual event should be considered an expected or unexpected event.

Note the “illustration” in the lower part of the table!

<b><i>Current Labeling</i></b>	<b><i>AE/Patient Presents</i></b>	<b><i>Answers:</i></b>
<i>Allergic Phenomena</i>	<i>Repetitive Sneezing</i>	<i>Expected</i>
<i>Anemia</i>	<i>Aplastic anemia on Bone Marrow Biopsy</i>	<i>Unexpected</i>
<i>Blurred Vision</i>	<i>Cataract Formation</i>	<i>Unexpected</i>
<i>Confusion</i>	<i>Psychotic Depression</i>	<i>Unexpected</i>
<i>Elevated SGOT</i>	<i>Hepatitis</i>	<i>Unexpected</i>
<i>Hives</i>	<i>Urticaria</i>	<i>Expected</i>
<i>Phototoxic Reaction</i>	<i>Erythema After Sunlamp Exposure</i>	<i>Expected</i>
<i>Renal Dysfunction</i>	<i>Acute Renal Failure</i>	<i>Unexpected</i>
<i>Thrombocytopenia</i>	<i>Low Platelet Count</i>	<i>Expected</i>
<b><i>ILLUSTRATION:</i></b>		
<b><i>Current Labeling</i></b>	<b><i>AE/Patient Presents</i></b>	<b><i>Answers:</i></b>
<i>Hypotension</i>	<i>Anaphylactic Shock</i>	<i>Unexpected</i>
<i>Anaphylaxis</i>	<i>Hives, Hypotension Wheezing</i>	<i>Expected</i>

***Exercise: How would you describe an AE?***

Which event would not be considered “serious” under the current regulatory definition?

1. Fatality from a motor vehicle accident.
2. Attempted suicide.
3. Emergency room treatment for a fracture resulting from a fall.
4. Serious bleeding requiring multiple blood transfusions.

Answers: 3. Emergency room treatment is not considered hospitalization; 1. fatality is fatal; 2. attempted suicide is life-threatening; 4. serious bleeding requiring multiple transfusions is intervention to prevent a serious outcome.

***Exercise: How would you describe an AE?***

Example: A subject experiences a bleeding stomach ulcer that requires hospitalization. What event(s) should be listed on the Case Report Form (CRF)?

Answer: Bleeding stomach ulcer

# Section VIII: Appendices

**Appendices:**

- 1. www Resource Links**
- 2. DMID Clinical Terms of Awards (effective Oct. 1, 2002)**
- 3. Guidance on DMID Clinical Terms of Awards (effective Oct. 1, 2002)**
- 4. ICH Expedited Reporting**
- 5. DMID Source Documentation Guidelines**
- 6. DMID Adult Toxicity Tables (May 31, 2001)**
- 7. DMID Pediatric Toxicity Tables (May 31, 2001)**
- 8. WHO Toxicity Tables**
- 9. DMID Required Reporting and Guidelines for Serious Adverse Events**
- 10. DMID SAE Report Form**
- 11. Sample AE Form**
- 12. NIH Policy for Data and Safety Monitoring (June 10, 1998)**
- 13. Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials (NIH, June 5, 2000)**
- 14. Excerpt from ICTDR/ DMID Data Safety and Monitoring Report Template**