

Manual for Expedited Reporting of Adverse Events to DAIDS

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1. INTRODUCTION

The U.S. Code of Federal Regulations (CFR) defines procedures and requirements governing the use of investigational new agents regulated by the U.S. Food and Drug Administration (FDA), including the monitoring and reporting of serious adverse events (21 CFR 312). The Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID) provides clinical research funding and often serves as an IND sponsor. NIAID (DAIDS) is responsible for ensuring that its supported and/or sponsored research is conducted in accordance with the above regulation, other applicable CFRs, and both FDA and International Conference on Harmonisation (ICH) guidance documents.

This manual defines which adverse events (AEs) must be reported in an expedited manner to DAIDS to fulfill its regulatory obligations as a sponsor. DAIDS, as IND sponsor, must submit 7-day and 15-day IND Safety Reports to the FDA per 21 CFR 312.32 and safety information annually per 21 CFR 32.33. Two categories of expedited reporting to the DAIDS Safety Office will be used: 1) Serious Adverse Events (SAE) Reporting or 2) Suspected, Unexpected Serious Adverse Reactions (SUSAR) Reporting.

1.1 Scope

This manual applies to all DAIDS-supported and/or -sponsored clinical trials, unless the DAIDS Office for Policy in Clinical Research Operations (OPCRO) Director or designee has delegated the responsibility for expedited adverse event (EAE) reporting to another entity (e.g., a pharmaceutical or investigator-sponsor).

Except for exempted trials, investigators and site personnel for DAIDS-funded and/or -sponsored studies must follow the requirements and procedures for expedited reporting of AEs to DAIDS as described in this manual.

1.2 Purpose

The purpose of this manual is to:

- Define criteria used to characterize AEs,
- Identify which AEs require expedited reporting to the DAIDS Safety Office, and
- Define methods and timelines for reporting AEs to DAIDS in order to fulfill DAIDS' regulatory requirements to the FDA as a sponsor, as well as DAIDS' obligations to industry collaborators supplying study agent(s).

1.3 Responsibilities

Site investigators have the primary responsibility for AE identification, documentation, and assessment of severity and relationship to study agents. The medical personnel who perform these assessments must be directly involved in the clinical evaluation of the research subjects.

2. KEY ELEMENTS TO CHARACTERIZE ADVERSE EVENTS

Assessment of AEs is based on the following characteristics: seriousness, relationship of the AE to the study agent(s), expectedness of the AE, and severity (intensity) of the AE. Assessment of the expectedness of an AE with study agent(s) is performed only for the SUSAR Reporting category.

2.1 Seriousness

The ICH guidance, “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting,” (ICH E2A) defines a **serious adverse event (SAE)** as 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,
- Is a congenital anomaly/birth defect, or
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

2.2 Relationship to Study Agent

The site investigator is responsible for assessing the relationship between the AE and the study agent(s). Site investigators must determine whether there is a **reasonable possibility** that the study agent(s) caused or contributed to a SAE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and administration of the study agent(s),
- A plausible biological mechanism for the agent to cause the AE,
- Another possible etiology for the AE,
- Previous reports of similar AEs associated with the study agent or other agents in the same class, and
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable.

The terms used to assess the relationship of an event to study agent are:

- **Related** – There is a reasonable possibility that the AE may be related to the study agent(s).
- **Not Related** – There is not a reasonable possibility that the AE is related to the study agent(s).

When a SAE is assessed as “not related” to study agent(s), an alternative etiology, diagnosis, or explanation for the SAE should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated, as required.

When the study agent is a fixed dose combination agent, an assessment of attribution will be made for each component and the combination agent.

2.3 Expectedness

Expected AEs are AEs that have been previously observed with use of the study agent(s) and are listed in the package insert or Investigator's Brochure. Expectedness is not based on what might be anticipated from the pharmacological properties of the study agent.

Unexpected AEs are AEs for which the nature or severity (intensity) is not consistent with the applicable agent information (Investigator's Brochure, package insert, or summary of agent characteristics).

2.4 Severity (Intensity)

In order to maintain consistency among clinical trials and clinical research sites for evaluating the severity of an AE, DAIDS developed a table of common clinical and laboratory AEs. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is located on the DAIDS Safety Office website at <https://rsc.tech-res.com/>. The severity of the parameters listed in the table ranges from grade 1 (mild) to grade 4 (potentially life-threatening). Death is defined as grade 5 severity.

Unless stated otherwise in the protocol, study staff is required to use the DAIDS AE Grading Table to determine the severity of the AE. The protocol will specify the Grading Table to be used for the trial. Specific protocols may include additional or modified criteria for grading AEs that are not included in the DAIDS AE Grading Table. All events reported to DAIDS in an expedited fashion must be graded for severity.

2.5 Severity vs. Seriousness of Adverse Events

The term "severity" describes the intensity of a specific event. The severity of a specific event is graded, i.e., mild (Grade 1), moderate (Grade 2), severe (Grade 3), potentially life-threatening (Grade 4), or death (Grade 5) using the DAIDS AE Grading Table. The severity of an AE does not determine whether an event meets the definition of seriousness, which is based on participant/event *outcome or action* criteria associated with events that pose a threat to a participant's life or functioning (ICH E2A).

3. ADVERSE EVENTS REQUIRING EXPEDITED REPORTING

The protocol will specify one of the two categories of AEs to be reported to DAIDS in an expedited fashion. Either reporting category of 1) all SAEs or 2) only SUSARs will be approved by DAIDS. The choice of category is based on several considerations regarding the clinical trial, including the following: whether or not the study agent(s) have been approved by the U.S. FDA for the indication that is under evaluation in the trial, the degree of risk that may be associated with the study agent(s), and/or the trial strategy, etc.

3.1 SAE (Serious Adverse Event) Reporting Category (Appendix A)

Report any AE following any exposure to the study agent that:

1. Results in death,
2. Is life-threatening, (*The term “life-threatening” 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.*)
3. Requires inpatient hospitalization or prolongation of existing hospitalization, (*Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event.*)

*The following types of hospitalization do **not** require expedited reporting to DAIDS:*

- *Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep),*
- *Protocol-specified admission (e.g., for a procedure required by protocol), or*
- *Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (NOTE: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would therefore be reportable.)*

4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect,
 - *Clinically insignificant physical findings at birth, including those regarded as normal variants, do not meet reporting criteria. If a clinically significant anomaly is reported, all other findings (including those of no individual significance) should be included in the same report. For example, an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant with no other findings would not be reported as an SAE, but polydactyly or Mongolian spot occurring with a major cardiac defect would be reported and included in the SAE report.*

- *Information about congenital anomalies can be found on the Centers for Disease Control and Prevention (CDC) website:
<https://www.cdc.gov/ncbddd/birthdefects/research-tools.html> – Guidelines for Conducting Birth Defects Surveillance, National Birth Defects Prevention Network (NBDPN), appendix 3.1. Direct link to document:
http://www.nbdpn.org/docs/Appendix_3_1_BirthDefectsDescriptions2015_2016DEC14.pdf This website listing should not restrict the reporting of anomalies that the site investigator deems important for the sponsor to know.*

6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include the following: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; etc.

3.2 Suspected, Unexpected Serious Adverse Reactions (SUSAR) Reporting Category (Appendix B)

Instead of the SAE reporting category, some non-IND studies/trials using U.S. FDA-approved agents with approved dosages for approved indications in typical populations may, at the discretion of DAIDS, use the SUSAR reporting category. An SAE with onset after exposure to study agent(s) will be reported if the SAE fulfills the following criteria:

- Related (see Section 2.2), and
- Unexpected (see Section 2.3).

3.3 Other Protocol-Defined Reporting

In addition to specifying one of the reporting categories listed above, a protocol may require other AEs to be reported on an expedited basis. In this case, the protocol will explicitly identify the additional AEs to be reported to DAIDS.

4. ADDITIONAL EXPEDITED REPORTING SPECIFICATIONS

4.1 Reporting Period

The protocol-specified reporting period continues from enrollment of a trial participant to the end of trial follow-up for that participant. When the protocol requires the same reporting category of AEs to be reported in an expedited manner beyond the trial follow-up for each participant, then the protocol must specify the duration of this additional reporting period.

After the **protocol-defined AE reporting period**, unless otherwise noted, only SUSARs will be reported to DAIDS if the study staff becomes aware of the events on a passive basis (from publicly available information).

4.2 Adverse Events Not Requiring Expedited Reporting to DAIDS

- An SAE occurring **before** exposure to a study agent.
- Immune reconstitution inflammatory syndrome (IRIS), even if the event otherwise meets the reporting criteria. IRIS is an intense immune reaction that may result from a response to HIV treatment and is an anticipated event for antiretroviral therapies.

4.3 Submission of Updated Information on Expedited Adverse Events

Sites must follow each AE until the AE is resolved or stable. For each AE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. The following are examples that must be submitted:

- An updated report documenting the stable or resolved outcome of the AE, unless the initial report included a final outcome,
- Any change in the assessment of the severity grade of the AE or the relationship between the AE and the study agent, or
- Additional significant information on a previously reported AE (e.g., cause of death, results of re-challenge with the study agent(s)).

4.4 Reporting Recurrent Adverse Events on an Expedited Basis

For an event previously reported to the DAIDS Safety Office, if the AE fully resolved but then reoccurs with an outcome meeting expedited reporting criteria, the AE must be reported as a new initial report to the DAIDS Safety Office.

5. METHODS AND TIMEFRAME FOR EXPEDITED REPORTING

5.1 Electronic Transmission of Adverse Events that Require Expedited Reporting

All information should be submitted through the DAIDS Adverse Experience Reporting System (DAERS), once DAERS has been implemented at a clinical research site.

If DAERS has not been implemented at a clinical research site or a clinical research site has difficulty accessing the DAERS system at the time an AE must be reported, the DAIDS Expedited Adverse Event Reporting Form (EAE Form) should be used. This form can be found at the website for the DAIDS Safety Office at <https://rsc.tech-res.com/>. All information requested on the EAE Form must be provided and the form faxed or e-mailed as an attachment to the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided in Appendix C.

5.2 Timeframe for Expedited Adverse Event Reporting to DAIDS

The timeframe for expedited reporting of individual AEs begins when the clinical research site recognizes that **an event fulfills the protocol-defined criteria for expedited reporting to DAIDS**. Clinical research sites must submit AEs to the DAIDS Safety Office immediately, **and no later than 3 reporting days** (Monday through Friday, see complete definition in Appendix D) after the site becomes aware of an event that meets protocol-defined criteria for expedited reporting.

5.3 Site Investigator Assessment and Signature

A site physician investigator or sub-investigator listed on the Form FDA 1572 for IND studies or the DAIDS Investigator of Record (IoR) Agreement for non-IND studies must review and verify the completed EAE form or DAERS report for accuracy and completeness and then sign the report. This physician also makes the site's final assessment of the relationship between the study agent(s) and the SAE.

In the rare event that such physician(s) are not available for signature, sites may submit the AE requiring expedited reporting without the signature to meet reporting timeframe requirements. However, the completed EAE report (whether the EAE form or DAERS report) with signature and any necessary corrections or additions must be submitted within the next 3 reporting days (see definition in Appendix D). The IoR or designee is responsible for designating at least one other physician at the site who can perform the assessment and signature so as to provide uninterrupted coverage of monitoring of AEs that will require expedited reporting.

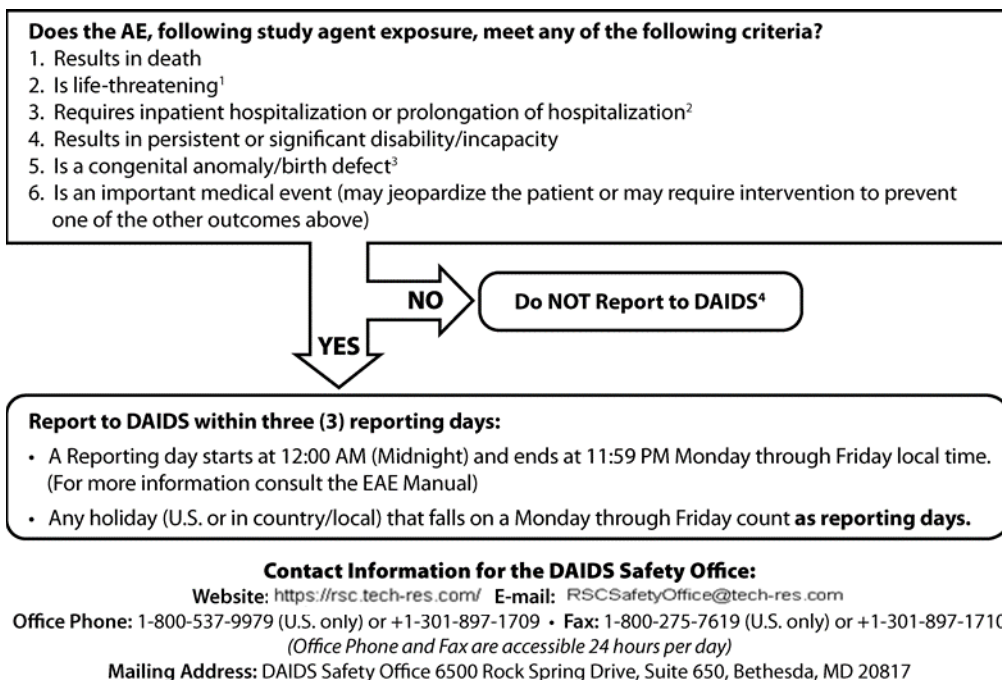
6. EXPEDITED REPORTING PROCEDURES DEFINED IN THE PROTOCOL

In order to fully define the expedited reporting requirements for a clinical trial, the protocol document will specify the following:

- One of the two categories of AE Reporting (i.e., SAE or SUSAR) and any other AEs to be reported on an expedited basis,
- The study agent(s) that require assessment of relationship with the reported AE. Specified study agents may include those provided outside of the clinical trial,
- The duration of the protocol-defined expedited reporting period. The protocol will state either that the defined category of AE reporting is required until the end of trial follow-up for each participant or that this reporting period will be extended for a time (to be specified in the protocol) beyond the end of trial follow-up for each participant. The protocol will also state that SUSARs will be reported after the protocol-defined reporting period if the site staff becomes aware of the event on a passive basis (from publicly available information), and
- The version number of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events and any additional or modified protocol-specific grading criteria or tables that are to be used for the clinical trial.

7. APPENDICES

APPENDIX A: SAE (SERIOUS ADVERSE EVENT) REPORTING CATEGORY FLOW CHART



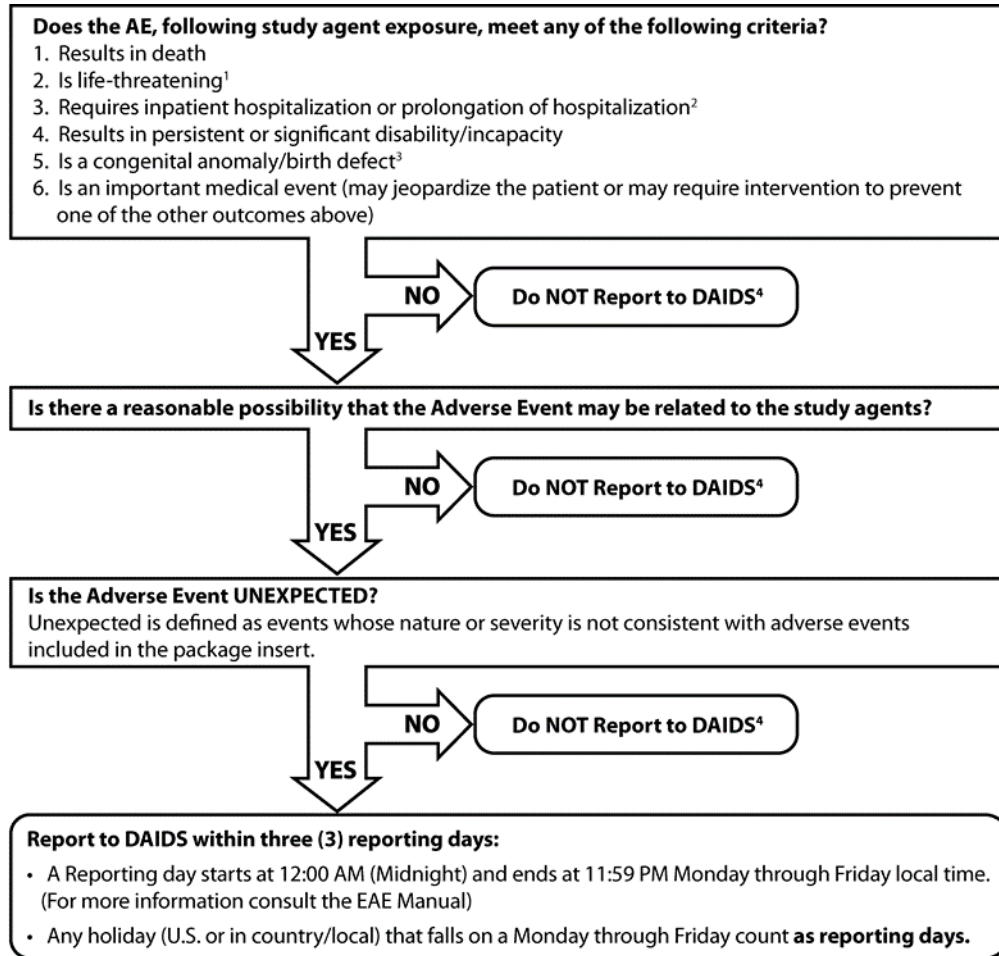
¹ “Life-threatening” refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

² Per ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT:** Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE:** A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

³ Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

⁴ Please ensure that any other protocol-specific reporting requirements are met.

**APPENDIX B:
SUSPECTED, UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)
REPORTING CATEGORY FLOW CHART**



Contact Information for the DAIDS Safety Office:

Website: <https://rsc.tech-res.com/> • E-mail: RSCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • Fax: 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

¹ “Life-threatening” 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 that hypothetically might have caused death if it were more severe.

² Per ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT:** Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator. (**NOTE:** A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

³ Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

⁴ Please ensure that any other protocol-specific reporting requirements are met.

**APPENDIX C:
CONTACT INFORMATION FOR DAIDS SAFETY OFFICE**

All reports of expedited adverse events are submitted to the DAIDS Safety Office.

For questions or other communication, please note the following:

Website:	https://rsc.tech-res.com/
Office Phone*:	1-800-537-9979 (U.S. only) or +1-301-897-1709
Office Fax*:	1-800-275-7619 (U.S. only) or +1-301-897-1710
Office Email:	RSCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM (U.S. Eastern Time)
Mailing Address:	DAIDS Safety Office 6500 Rock Spring Drive Suite 650 Bethesda, MD 20817

*Office phone and fax are accessible 24 hours per day.

APPENDIX D: DEFINITION OF TERMS

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a study agent and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) agent, whether or not related to the medicinal (investigational) agent. (ICH E2A) (Synonym: Adverse Experience)

Clinical Research Site: Discrete location (e.g., hospital, outpatient clinic, health maintenance organization, community health center, private practice, clinic, etc.) where qualified professionals conduct clinical trial research in accordance with Good Clinical Practices. (DAIDS)

Combination agent: Either a co-formulated product (lamivudine/zidovudine fixed drug combination) or agents that are given together to achieve the desired therapeutic effect (darunavir given with ritonavir).

DAERS: DAIDS Adverse Experience Reporting System is an internet-based application to facilitate the reporting and processing of AEs to and by the Division of AIDS.

DAIDS Safety Office: The Office to which AEs requiring expedited reporting are submitted. (DAIDS)

EAE Form: The Expedited Adverse Event (EAE) paper form to be completed if DAERS system is not available.

IND: An investigational new drug application. (21 CFR 312)

IND Safety Report: A written report from the IND sponsor notifying the FDA and study site investigator(s) participating in studies under the IND of an AE related to the study agent(s) that is both serious and unexpected.

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational agent(s) relevant to the study of the investigational agent(s) in human subjects. (ICH E6)

Non-IND Clinical Trial: A clinical trial for which there is no IND filed with the U.S. FDA. (DAIDS)

Package Insert: The approved package circular in marketed drug packaging containing the drug description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, dosage and administration, how drug is supplied, "clinical studies," and "references." (21 CFR 201.57)

Reporting Days: “Reporting days” are those that count toward the 3-day timeline provided for reporting of EAEs to DAIDS. The criteria used to determine reporting days are as follows:

- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time.
- A day is counted as a reporting day regardless of the time of day that awareness occurred. The day a site indicates that site personnel became aware of an EAE that meets reporting criteria shall count as day 1 if that day occurs on a reporting day (i.e., Monday through Friday). If that day occurs on a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.
- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.

Serious Adverse Event (SAE): 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. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E6 and E2A)

Site Investigator: A physician listed on the Form FDA 1572 for IND studies or on the DAIDS Investigator of Record (IoR) Agreement for non-IND studies who performs the assessment of relationship of AEs to study agent(s) for expedited reporting to DAIDS.

Study Agent: In regard to expedited reporting of AEs to DAIDS, drugs, biological agents, combination of drugs and biological agents or devices (approved or investigational) defined in the protocol as requiring assessment of relationship to AEs for expedited reporting to DAIDS. Specified study agents may include those provided outside of the clinical trial.

SUSAR: Suspected, Unexpected Serious Adverse Reaction is an event that is:

- Serious (see SAE definition above)
- Related (i.e., there is a reasonable possibility that the AE may be related to the study agent)
- Unexpected (see definition below)

Unexpected AE: An AE, the nature or severity (intensity) of which is not consistent with the applicable agent information (Investigator’s Brochure, package insert, or summary of agent characteristics). (DAIDS)

References:

Code of Federal Regulations, Title 21, Part 201.57: Specific requirements on content and format of labeling for human prescription drugs.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57>

Code of Federal Regulations, Title 21, Part 312.32: IND Safety Reports.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.32>

International Conference on Harmonisation Guideline for Industry: Clinical Safety Data Management: Definition

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

International Conference on Harmonisation Guideline for Industry: Good Clinical Practice: Consolidated Guideline

(E6).http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf