

POLICY
Expedited Adverse Event Reporting

Approval Date: 18 MAY 2016
Effective Date: 20 JUN 2016

No.: DWD-POL-CL-013.04

CHANGE SUMMARY NOTE: This policy has been reviewed for accuracy and updated to meet 508 compliance guidelines. Minor revisions have been made to the definitions section for clarity. The definitions included in this policy are applicable only to Expedited Adverse Events. The roles stated in this policy do not supersede other responsibilities associated with expedited reporting to DAIDS. This version supersedes version 3.0 dated 28 APR 2010.

1.0 PURPOSE

The purpose of this policy is to describe the requirements for reporting adverse events (AEs) in an expedited timeframe to the Division of AIDS (DAIDS).

2.0 SCOPE

This policy applies to all National Institute of Allergy and Infectious Diseases (NIAID) DAIDS-supported and -sponsored clinical trials unless the responsibility for expedited adverse event reporting has been delegated to another entity (e.g., a pharmaceutical company or investigator-sponsor) with concurrence from the DAIDS Office for Policy in Clinical Research Operations (OPCRO) Director or designee.

3.0 BACKGROUND

The collection and expedited reporting of AEs allows for a sponsor to monitor the safety of participants throughout the clinical trial. NIAID (DAIDS) is responsible for ensuring that its supported and/or sponsored research is conducted in accordance with all applicable regulations (e.g., 21 CFR Part 312) and both Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) guidance documents.

The *Manual for Expedited Reporting of Adverse Events to DAIDS*, commonly referred to as the DAIDS EAE Manual, provides clinical research sites with the requirements and procedures to report these events to DAIDS.

4.0 DEFINITIONS

The definitions included in this policy are applicable to DAIDS Expedited Adverse Events. For additional definitions, see [DAIDS glossary](#).

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

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medicinal (investigational) agent, whether or not related to the medicinal (investigational) agent. (DAIDS EAE Manual)

Expedited Adverse Event (EAE): An AE that meets the criteria for expedited reporting to DAIDS. (DAIDS EAE Manual)

EAE Reporting Days: The days that count toward the three day timeline provided for reporting of EAEs to DAIDS. Refer to the *Manual for Expedited Reporting of Adverse Events to DAIDS* for criteria used to determine reporting days. (DAIDS EAE Manual)

Investigational Device Exemption (IDE): An FDA exemption that allows an unapproved medical device to be used for investigational purposes. (21 CFR 812 and NIAID)

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. (DAIDS EAE Manual)

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." (DAIDS EAE Manual)

Serious Adverse Event (SAE): A Serious Adverse Event (SAE) is any untoward medical occurrence (i.e., an AE) that meets one or more of the following criteria for seriousness:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of an existing hospitalization,
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in a congenital anomaly or 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 subject or may require intervention to prevent one of the other outcomes listed above.

For additional information on SAEs, please refer to the DAIDS EAE Manual.

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Suspected Unexpected Serious Adverse Reaction (SUSAR): An AE that is:

- Serious (i.e., an SAE),
- Related (i.e., there is a reasonable possibility that the AE may be related to the study product), and
- Unexpected (i.e., an AE whose nature or severity [intensity] is not consistent with the applicable product information found in an investigator's brochure, a package insert or a summary of agent characteristics). (DAIDS EAE Manual)

Unexpected AE: An AE whose nature, severity (intensity), or frequency is not consistent with the applicable study product information (e.g., investigator's brochure, package insert, or summary of product characteristics). (DAIDS EAE Manual)

5.0 RESPONSIBILITIES

Site personnel

Site personnel includes all individuals involved in the conduct of a NIAID (DAIDS) clinical trial. These individuals must notify the IoR or designee of any AEs that meet the criteria for expedited reporting to DAIDS.

Investigator of Record

The Investigator of Record or their designee is the individual involved in the conduct of a NIAID (DAIDS) clinical trial, who is responsible for AE identification and documentation and for assessing AE severity and its relationship to a study product.

The IoR is also responsible for reporting all EAEs occurring at their CRS to the DAIDS RSC Safety Office as soon as possible and according to timeframes stipulated in the DAIDS EAE Manual. Before submitting a report, the IoR or designee must review and verify the completed EAE form or DAERS DAIDS Adverse Experience Reporting System (DAERS) report (whichever is applicable) for accuracy and completeness before signing it. If reports are submitted through DAERS, the IoR or designee must also complete and submit the Physician Electronic Signature Attestation Form to the DAIDS RSC Safety Office. For more information on this form, refer to the Expedited Reporting section on the [DAIDS RSC website](#).

The IoR or designee must designate at least one other physician at their CRS who can perform the assessment and sign off so as to provide uninterrupted coverage

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of monitoring of AEs that require expedited reporting to DAIDS.

Institution

An Institution is a public or private entity or agency engaged in research covered by 45 CFR Part 46 which is responsible for promptly reporting EAEs that are Unanticipated Problems to their IRB or EC (as applicable) and DAIDS, in addition to any other local reporting requirements.

DAIDS Medical Officer (MO)

DAIDS Medical Officers are responsible for monitoring safety in clinical trials where they serve on the team as the medical monitor. The DAIDS MO reviews the EAEs that are submitted to DAIDS and is responsible for making the determination of reportability to the FDA.

DAIDS Safety and Pharmacovigilance Team (SPT)

The DAIDS Safety and Pharmacovigilance Team monitors safety across all NIAID (DAIDS) clinical trials and facilitates the review of EAEs between the DAIDS RSC Safety Office and the DAIDS MO. The DAIDS SPT also maintains a distribution plan and tracking method for sending safety information to investigators, other collaborators, and pharmaceutical sponsors.

DAIDS Regulatory Affairs Branch

The DAIDS Regulatory Affairs Branch ensures that DAIDS fulfills its regulatory obligations as a sponsor for any studies conducted under an IND or IDE.

Director of OPCRO or designee

Under circumstances when an exception to the EAE policy has been requested, the Director of OPCRO or designee will make the final decision regarding the exception.

6.0 POLICY

The IoR or designee will follow the policy on reporting adverse events that meet the criteria for expedited reporting to DAIDS. See the DAIDS EAE Manual for instructions and additional information on the reporting process

- 6.1 All protocols for clinical trials must follow the requirements and procedures for reporting adverse events in an expedited manner as described in the latest version of the DAIDS EAE Manual. Ongoing studies may continue the use of legacy reporting manuals and systems until such time as they have been instructed to switch to the most current manual.

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- 6.2 The expedited reporting section of a protocol must contain the following information:
 - a. The reporting category to be used (i.e., either SAE or SUSAR) and any additional protocol-specific reporting requirements,
 - b. The study product(s) and/or intervention(s) for which expedited reporting to DAIDS is required,
 - c. The duration of the protocol-defined expedited reporting period (typically from study enrollment to completion or discontinuation). If an extended follow-up period after study completion or discontinuation is warranted, this must be specified in the protocol.
 - d. The version number of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) and any additional or modified protocol-specific AE grading tables that will be used in the study.
- 6.2.1 If there is no reporting of expedited events to DAIDS, the protocol will specify the party responsible for receipt, review, and regulatory submission of expedited event reports
- 6.2.2 Specific protocols may include additional or modified criteria for AEs that are not included in the DAIDS AE Grading Table.
- 6.2.3 Where local laboratory normal values may differ from the DAIDS AE Grading Table, exception from using the DAIDS AE Grading Table for local laboratory values may, with justification, be sought from DAIDS directly or through the Scientific Review Committee process.
- 6.3 For sites where DAIDS Adverse Experience Reporting System (DAERS) has been implemented, all EAEs and supporting information will be submitted to DAIDS using DAERS, unless the system is unavailable for technical reasons.
 - 6.3.1 For sites where DAERS has not been implemented, all EAEs and supporting information will be submitted to DAIDS using the DAIDS EAE form.
- 6.4 EAEs must be submitted to DAIDS within the three day reporting time period specified in the DAIDS EAE Manual.
- 6.5 EAEs and all supporting information submitted to DAIDS must be in English.

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Non-English supporting documents must be translated into English before submission.

- 6.6 Any exception to this policy must be approved in writing by the Director of OPCRO or designee.
- 6.7 This policy does not supersede other responsibilities of an investigator, awardee institution, IRB or EC where EAEs are concerned.

7.0 REFERENCES

[International Conference on Harmonisation Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting \(E2A\)](#)

[International Conference on Harmonisation Guideline for Industry: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting \(E2D\)](#)

[International Conference on Harmonisation Guidance for Industry, Guideline for Good Clinical Practice \(E6\)](#)

[Code of Federal Regulations, Title 21 CFR Part 56 \(Institutional Review Boards\)](#)

[Code of Federal Regulations, Title 21 CFR Part 312 \(Investigational New Drug Application\)](#)

[Code of Federal Regulations, Title 21 CFR Part 812 \(Investigational Device Exemptions\)](#)

[Code of Federal Regulations, Title 45 CFR Part 46 \(Protection of Human Subjects\)](#)

[NIAID Clinical Terms of Award](#)

[DAIDS RSC Safety Office](#)

[Manual for Expedited Reporting of Adverse Events to DAIDS](#)

[DAIDS AE Grading Table](#)

[DAIDS EAE Form](#)

[DAIDS Protocol Template for Expedited Reporting](#)

[DAIDS Physician Electronic Signature Attestation Form](#)

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[OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)

8.0 INQUIRIES

Questions and comments regarding this SOP may be directed to the [OPCRO Policy Group](#).

9.0 AVAILABILITY

This policy is available electronically on the [Division of AIDS \(DAIDS\) Clinical Research Policies and Standard Procedures](#) webpage.

10.0 APPENDICIES

None

11.0 APPROVAL

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Director, Office for Policy in Clinical Research Operations (OPCRO)