

ARCHIVED POLICY

Expedited Adverse Events Reporting

Approval Date: 28 APR 2010
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No.: DWD-POL-CL-013.03

CHANGE SUMMARY: This Policy has been reviewed for accuracy and updated to meet 508 compliance guidelines. Roles stated in this policy do not supersede other responsibilities associated with EAE's. Key changes include expanding the responsibilities section to provide clarification of site personnel, Investigator of Record (IoR), institution, and DAIDS staff responsibilities. Additional modifications include an alternate EAE reporting pathway as stated in section 6.2.1, information pertaining to local laboratory normal values, and use of the DAIDS Adverse Experience Reporting System (DAERS). This version supersedes version 2.0 dated 20 DEC 06.

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/or -sponsored clinical trials unless the responsibility for expedited adverse events (EAE) 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 FDA and International Conference on Harmonisation (ICH) guidance documents.

The *Manual for Expedited Reporting of Adverse Events to DAIDS* has been developed to provide sites with the requirements and procedures to report these events to DAIDS.

4.0 DEFINITIONS

Adverse Event (AE): 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. (Modified from ICH E2A)

Clinical Trial: A prospective study of human subjects designed to answer questions about biomedical or behavioral interventions, e.g., drugs, treatments, devices, or new ways of using known treatments to determine whether they are safe and effective. (NIAID)

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

DAIDS Regulatory Support Contract (RSC): A contract that provides clinical, regulatory, and technical support services for NIAID (DAIDS)-supported and/or -sponsored clinical trials. (DAIDS)

DAIDS RSC Safety Office: The office contracted to receive expedited adverse event reports that are submitted to DAIDS. (DAIDS)

Expedited Adverse Event: An adverse event that meets the criteria for expedited reporting to DAIDS. (DAIDS)

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

EAE Reporting Days: The days that count toward the 3-day timeline provided for reporting of EAEs to DAIDS. See DAIDS EAE Reporting manual for criteria used to determine reporting days. (DAIDS)

Investigator of Record (IoR): The individual at the Clinical Research Site (e.g., site investigator) responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an IND or the DAIDS Investigator of Record Agreement for non-IND studies. (DAIDS)

Investigational Device Exemption (IDE): Similar to an IND, allows an unapproved medical device to be used for investigational purposes. For more information, go to 21 CFR Part 812 and NIAID Human Subjects Resources portal. (NIAID)

Investigational New Drug: (IND): A drug or biological product that is used in a clinical investigation. The terms "investigational new drug" and "investigational agent" are deemed to be synonymous within DAIDS policies. (DAIDS)

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. (Modified from ICH E6)

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)

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)

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 expedited adverse event reporting to DAIDS. Specified study agents may include those provided outside of the clinical trial. (DAIDS)

Suspected Unexpected Serious Adverse Reaction (SUSAR): a SUSAR is an event that is:

1. Serious (See SAE definition);
2. Related (i.e., there is a reasonable possibility that the AE may be related to the study agent); *and*
3. Unexpected (See unexpected AE definition) (DAIDS)

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

For additional definitions see DAIDS Glossary:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Glossary.htm>.

5.0 RESPONSIBILITIES

Site personnel

Site personnel (anyone involved in the conduct of a NIAID [DAIDS] clinical trial) must notify the *IoR or designee* of any adverse events that meet the criteria for expedited adverse event reporting.

Investigator of Record

The *Investigator of Record (IoR) or designee* is responsible for AE identification, documentation, and assessment of severity and relationship to study product. The IoR is also responsible for reporting all EAEs occurring at the clinical research site to the DAIDS Safety Office as soon as possible, and according to timeframes identified in the *Manual for Expedited Reporting of Adverse Events to DAIDS*. Prior to submitting the report, the IoR or designee must verify the completed EAE form or DAERS report for accuracy and completeness and sign the report. The IoR or designee must designate 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.

Institution

For purposes of this policy, an *institution* is a public or private entity or agency engaged in research covered by 45 CFR Part 46.

Some EAEs will also meet the criterion for an Unanticipated Problem involving risk to subjects or others¹. An Unanticipated Problem is an event that warrants consideration of substantive changes to the protocol, informed consent process/document, or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. The *institution* is responsible to promptly report EAEs that are Unanticipated Problems to, among others, the Institutional Review Board (IRB)/Ethics Committee (EC) and DAIDS.

¹ 45 CFR §46.103(b)(5)(i) and 21 CFR §56.108(b)(1)

DAIDS Medical Officer (MO)

DAIDS MOs are responsible for monitoring safety in clinical trials where they serve on the team as the DAIDS MO.

DAIDS Safety and Pharmacovigilance Team

The *DAIDS SPT* monitors safety across all DAIDS clinical trials and performs sign off of safety reports after DAIDS MO review.

DAIDS staff

DAIDS staff will maintain a distribution plan and tracking method for sending Investigational New Drug (IND) Safety Reports and MedWatch reports to DAIDS investigators, other collaborators and pharmaceutical sponsors.

DAIDS Regulatory Affairs Branch (RAB)

The *DAIDS RAB* ensures that DAIDS fulfills its IND obligations.

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 *Manual for Expedited Reporting of Adverse Events to DAIDS*² 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 most current DAIDS reporting 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.

² <http://rcc.tech-res.com/safetyandpharmacovigilance/>

6.2 The expedited reporting section of the protocol must contain the following information:

1. Reporting category (i.e., SAE, SUSAR)
2. Study agent(s)
3. Grading table
4. Reporting period

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 table.

6.2.3 Where local laboratory normal values may differ from the DAIDS Grading Table, exception to use of the DAIDS 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 DAERS has been implemented, all EAEs and supporting information will be submitted to DAIDS using the 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 time period specified in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

6.5 EAEs and all supporting information submitted to DAIDS must be in English. Non-English supporting documents must be translated into English before submission.

6.6 Any exception to the EAE 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, or Institutional Review Board (IRB)/Ethics Committee (EC) associated with expedited adverse events.

7.0 REFERENCES

International Conference on Harmonisation Guideline for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A) <http://www.ich.org/LOB/media/MEDIA-436.pdf>

Draft International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting (E2D) http://www.ich.org/MediaServer.jserv?@_ID=631&@_MODE=GLB

International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guideline (E6) <http://www.fda.gov/oc/gcp/guidance.html>

Code of Federal Regulations, Title 21 CFR Part 56, Institutional Review Boards http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr56_06.html

Code of Federal Regulations, Title 21 CFR Part 312, Investigational New Drug Applications <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312>

Code of Federal Regulations, Title 21 CFR Part 812, Investigational Device Exemptions <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812>

Code of Federal Regulations, Title 45 CFR Part 46 Protection of Human Subjects <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

NIAID Clinical Terms of Award <http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf>

DAIDS Expedited Adverse Event Reporting Materials (e.g., Expedited Reporting Manual, AE Grading Table, and EAE Form) <http://rcc.tech-res.com/safetyandpharmacovigilance/>

DAIDS template wording for the EAE reporting section <http://rcc.tech-res.com/protocoldevelopmentinformation/>

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
<http://www.hhs.gov/ohrp/policy/AdvEvtntGuid.pdf>

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at: NIADOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically on the following URL:

<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Safety.aspx>

10.0 CHANGE SUMMARY

This policy supersedes version 2.0 dated 20 Dec 2006.

11.0 APPENDICES

None

12.0 APPROVAL

/Richard Hafner, MD/
Richard Hafner