

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

1.0 PURPOSE

The purpose of this policy is to provide guidance to investigators and site personnel conducting National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) -supported and/or -sponsored clinical research on collecting information pertaining to a suspected critical event and identifying and classifying the critical events so that appropriate actions can be initiated.

2.0 SCOPE

This policy applies to critical events involving NIAID (DAIDS) -supported and/or -sponsored clinical research sites.

3.0 BACKGROUND

Events can occur in the process of conducting clinical research that deviate from the Institutional Review Board (IRB)/Ethics Committee (EC)-approved protocol. Such events are considered protocol noncompliance. Deviations from the IRB/EC-approved protocol and other events, such as unanticipated problems, may adversely affect the risk to participants or others or have a significant adverse impact on study outcomes or integrity. Collectively, DAIDS calls such events, "Critical Events". For purposes of this policy, critical events include the following classes:

- Unanticipated Problems
- Serious or Continuing Noncompliance
- Suspension or Termination of IRB/EC Approval
- Suspected Research Misconduct

All NIAID (DAIDS) -supported and/or -sponsored clinical research falls under the reporting requirements of applicable U.S. regulatory agencies, including the Office for Human Research Protections¹ (OHRP) and the Office of Research Integrity² (ORI³). Some of this research is also subject to the U.S. Food and Drug Administration⁴ (FDA) reporting requirements. Although as a sponsor DAIDS is not responsible for reporting critical events to the applicable regulatory agencies, DAIDS has developed a

¹ 45 CFR 46

² 42 CFR 93

³ The Office of Research Integrity (ORI) is an office within HHS that promotes integrity in biomedical and behavioral research supported by the Public Health Service by monitoring institutional investigations of research misconduct and facilitating the responsible conduct of research.

<http://ori.dhhs.gov/>

⁴ 21 CFR 56

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

set of policies and manual to provide guidance on DAIDS and relevant regulatory agency requirements for reporting critical events.

These events may be identified by many individuals, including investigators, site personnel and IRB/EC members, through many different mechanisms. This policy identifies the Principal Investigator (PI) and/or designee who is responsible for collecting information and identifying and classifying the critical event(s) so appropriate actions can be initiated.

This policy directs investigators and site personnel to the appropriate section(s) of the DAIDS Critical Events Manual for instructions regarding the occurrence of specific critical events.

4.0 DEFINITIONS

Adverse event (AE): Any untoward or unfavorable medical occurrence in a human subject⁵, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.⁶ (OHRP)

Allegation: A disclosure of possible research misconduct through any means of communication. The disclosure may be by written or oral statement or other communications. (ORI)

Awardee: The institution receiving a grant, cooperative agreement, or contract that assumes legal, financial, and scientific responsibility for the funds and research. (DAIDS)

Continuing noncompliance⁷: A pattern of actions or omissions to act that suggests a future likelihood of reoccurrence and indicates an inability or unwillingness to comply with applicable laws, regulations or the requirements or determinations of the IRB/EC. (DAIDS)

Critical event: Any unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact

⁵ The terms subject and participant are used interchangeably in this policy

⁶<http://www.hhs.gov/ohrp/policy/advevntguid.pdf>

⁷ 45 CFR §46.103(b)(5)(i) and 21 CFR §56.108(b)(2)

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

on study outcomes or integrity. A single incident that is determined to be a critical event may represent more than one class of critical event. (DAIDS)

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

Note: An EAE can only occur after a participant receives a study agent. See the Manual for Expedited Reporting of Adverse Events to DAIDS⁸ for further information.

Fabrication: Making up data or results and recording or reporting them. (ORI)

Falsification: Manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record. (ORI)

Plagiarism: Using another person's ideas, processes, results, or words as one's own without giving credit. (ORI)

Protocol deviation/violation: An unplanned excursion from the protocol that is not implemented or intended as a systematic change. Protocol deviation is also used to refer to any other, unplanned instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations⁹. (DAIDS)

Reasonable Possibility: There is evidence to suggest a causal relationship between the research procedures and the adverse event, incident, experience, or outcome.¹⁰ (DAIDS)

Research misconduct¹¹: Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Research misconduct does not include honest error or differences of opinion. (ORI)

⁸ Manual available at http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Manual_for_Expedited_Reporting_AEs_to_D AIDS_v2.pdf

⁹modified from the definition of protocol deviation in the 2008 FDA Compliance Program Guidance Manual
bioresearch monitoring

¹⁰ Modified from FDA's definition at 21 CFR 312.32

¹¹ 42 CFR §93.103

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

Serious noncompliance¹²: An event that occurs within the context of the research that indicates a serious breach in compliance with applicable laws, regulations, or the requirements or determinations of the IRB/EC and results in an increased risk (i.e., physical, psychological, safety, privacy) to or compromises the rights and welfare of research participants. (DAIDS)

Subawardee: The entity to which a subaward (e.g., subcontract) is made and which is accountable to the awardee for the use of the funds provided. Subawardees must adhere to NIH and NIAID administrative requirements.¹³ (DAIDS)

Suspension of IRB approval¹⁴: An IRB/EC action to temporarily withdraw approval for part or all of a study, which results in stopping some or all of the study-related activities. (DAIDS)

Termination of IRB approval¹⁵: An IRB/EC action to permanently withdraw approval for a study which results in stopping the research and all study-related activities. (DAIDS)

Unanticipated problems involving risk to subjects or others¹⁶: Any incident, experience, or outcome that meets all of the following criteria:

1. unexpected given the research procedures that are described in the protocol-related documents; and the characteristics of the subject population being studied;
2. reasonable possibility of being related to a subject's participation in the research; and
3. suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.¹⁷ (OHRP)

For examples of incidents that represent different classes of critical events, see The DAIDS Critical Events Manual, Appendix A.

For additional definitions, see DAIDS Glossary:

¹² 45 CFR §46.103(b)(5)(i) and 21 CFR §56.108(b)(2)

¹³ Modified from the [Office of Research Integrity's Responsible Conduct of Research glossary](#)

¹⁴ 45 CFR §46.103(b)(5)(ii) and 21 CFR §56.108(b)(3)

¹⁵ 45 CFR §46.103(b)(5)(ii) and 21 CFR §56.108(b)(3)

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

¹⁷ <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.pdf>

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

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

5.0 RESPONSIBILITIES

Site personnel

Site personnel (anyone involved in the conduct of DAIDS -supported and/or -sponsored clinical research) must notify the PI and/or designee (e.g., Investigator of Record (IoR), Clinical Research Site (CRS) Leader) of any suspected critical events. When the site personnel cannot notify the PI and/or designee for fear of retribution or another reason, the site personnel must notify an appropriate person within their institution or DAIDS.

Principal Investigator (PI)

The *PI and/or designee* will gather appropriate information and determine if the event meets the criteria for one or more critical events as defined in this policy. Upon determination that one or more critical events have occurred at his/her site, the PI and/or designee will follow the applicable sections of the DAIDS Critical Events Manual: Unanticipated Problems Involving Risk to Participants or Others, Serious or Continuing Noncompliance, Suspension or Termination of IRB/EC Approval, and Research Misconduct.

Awardee Institution

The *awardee institution* is responsible for determining whether a report of suspected or alleged fabrication, falsification, or plagiarism represents research misconduct.

Note: This section does not alter an institution's responsibilities that has received NIAID (DAIDS) support for clinical research in accordance with the terms of grant award.

DAIDS staff member

For purposes of this policy, the *DAIDS staff member* is: a Program Officer, Medical Officer, or Contracting Officer's Representative (COR). For network related issues, a member from Program will generally be the lead. For site related issues, a member from the Office of Clinical Site Oversight (OCSO) will generally be the lead.

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

The *DAIDS staff member* notified of the suspected critical event will gather information from the site and will refer to the Critical Events: DAIDS Responsibilities policy for further actions.

6.0 POLICY

The awardee and subawardee institutions will follow the strictest requirement for reporting critical events, including U.S. Federal, State, country, local laws and regulations, and institutional policies. See the DAIDS Critical Events Manual for additional information on reporting critical events.

6.1 Site initial actions

- a. Any site personnel who becomes aware of a suspected or alleged critical event occurring at their site will notify the PI and/or designee within 24 hours¹⁸ of becoming aware of the incident.

Under circumstances in which the site personnel cannot notify the PI and/or designee for fear of retribution or another reason, the site personnel will notify an appropriate person within their institution or a DAIDS staff member responsible for the grant, contract, or protocol.

Site personnel will follow DAIDS policy for Source Documentation and their institution's procedures to document information as appropriate.

- b. A single event may represent more than one class of critical event. The PI and/or designee will review the Critical Events Classification criteria below and determine which critical event(s) occurred.

6.2 Critical Events Classifications

- a. An *unanticipated problem (UP)* has occurred when the event:
 1. is unexpected, given the research procedures that are described in the protocol-related documents and the characteristics of the participant population being studied; *and*
 2. is related or there is a reasonable possibility that the event is related to participation in the research; *and*

¹⁸ See the Critical Events Manual for reporting timeframes to DAIDS

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

3. suggests that the research places the participant(s) or others at a greater risk of harm than was previously known or recognized.¹⁹

For an event that is an UP, follow the Unanticipated Problems section in the DAIDS Critical Events Manual for further action.

Note: An adverse event is also an unanticipated problem when it meets the unanticipated problems criteria. See the DAIDS Critical Events Manual, Appendix B for additional information when determining which adverse events are unanticipated problems. Adverse events that also meet the criteria of an Expedited Adverse Event (EAE) must be reported to DAIDS in accordance with the DAIDS EAE Manual.

- b. *Serious noncompliance* has occurred when the event:
 1. Indicates that applicable laws, regulations, or the requirements or determinations of the IRB/EC were not followed; *and*
 2. Increases the risk to the participant or compromises the research participant's rights and welfare.

Continuing noncompliance has occurred when the event:

1. Reflects a pattern of actions or omissions to act in the conduct of the study that suggest a future likelihood of recurrence; *and*
2. Indicates an inability or unwillingness to comply with the applicable laws, regulations, or the requirements or determinations of the IRB/EC.

For an event that is serious or continuing noncompliance, follow the Serious or Continuing Noncompliance section of the DAIDS Critical Events Manual for further action.

- c. *Suspension or termination of IRB/EC approval* qualifies as a critical event when:

¹⁹<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

1. The IRB/EC temporarily or permanently withdraws its approval for part (e.g., suspending new enrollment in one arm of the research) or all of the approved research; and
2. The event is associated with:
 - a. research not being conducted in accordance with the IRB/EC's requirements *or*
 - b. unexpected serious harm to participants²⁰.

For an event that is a suspension or termination of IRB/EC approval, follow the Suspension or Termination of IRB/EC Approval section of the DAIDS Critical Events Manual for further action.

- d. *Research misconduct* may have occurred when there is an:
 1. Allegation of fabrication;
 2. Allegation of falsification; or
 3. Allegation of plagiarism.

For an event that meets one or more of the research misconduct criteria above, follow the Suspected Research Misconduct section of the DAIDS Critical Events Manual for further action.

Note: The awardee institution is responsible for determining whether reports of suspected or alleged fabrication, falsification, or plagiarism represent research misconduct. DAIDS staff are not responsible for the determination of whether a suspected or alleged critical event represents research misconduct.

²⁰<http://www.hhs.gov/ohrp/policy/continuingreview2010.pdf>

DAIDS
Bethesda, MD, USA

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

7.0 REFERENCES

HHS regulations for the Protection of Human Subjects at 45 CFR 46,

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

FDA regulations on Institutional Review Boards at 21 CFR 56,

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=56>

FDA regulations on Investigational New Drug Applications at 21 CFR 312,

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312>

FDA regulations on Investigational Device Exemptions at 21 CFR 812,

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812>

PHS Policies on Research Misconduct at 42 CFR 93,

http://ori.dhhs.gov/documents/42_cfr_parts_50_and_93_2005.pdf

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events,

<http://www.hhs.gov/ohrp/policy/advevntguid.pdf>

Guidance for Industry, Good Clinical Practice E6,

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129515.pdf>

Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse event reporting to IRBs,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf>

NIAID Research Misconduct Cases SOP,

<http://www.niaid.nih.gov/researchfunding/sop/pages/misconduct.aspx>

DAIDS policy on Requirements for On-Site Monitoring of DAIDS Supported and/or Sponsored Clinical Trials,

http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/onsitemonitor_reqs.pdf

DAIDS
Bethesda, MD, USA

POLICY

Identification and Classification of Critical Events: Site Responsibilities

Approval Date: 22 MAY 2012
Effective Date: 22 JUN 2012

No.: DWD-POL-RA-017.01

OHRP Guidance on Continuing Review of Research,
<http://www.hhs.gov/ohrp/policy/continuingreview2010.pdf>.

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

8.0 INQUIRIES

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

9.0 AVAILABILITY

This policy is available electronically at:
<http://www.niaid.nih.gov/labsandresources/resources/daidsclnrsrch/Pages/Default.aspx>

10.0 CHANGE SUMMARY

This policy is the first version. It does not supersede any other version.

11.0 APPENDICES

Critical Events Manual Appendix A-Examples of Critical Events
Critical Events Manual Appendix B-Determining Which Adverse Events are Unanticipated Problems

12.0 APPROVAL

/Scott Proestel, M.D./
Scott Proestel