

Critical Events Manual

Division of AIDS (DAIDS)

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I. Introduction

A. Purpose

The DAIDS Critical Events Manual guides investigators, site personnel, and DAIDS staff on required procedures to follow, including reporting to required entities, when one or more classes of critical events have been identified.

B. Scope

This manual applies to all National Institute of Allergy and Infectious Diseases (NIAID) (DAIDS) -supported and/or -sponsored clinical research.

C. 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”.

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 Protections (OHRP) and the Office of Research Integrity (ORI). Some of this research is also subject to the U.S. Food and Drug Administration (FDA) reporting requirements.

Unanticipated Problems

The U.S. Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(5)(i) and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66 require institutions to promptly report *unanticipated problems (UP) involving risks to participants or others* to certain entities including the IRB/EC, appropriate institutional officials, the department or agency head¹, the OHRP and, when applicable, the FDA.

¹ DAIDS is serving on behalf of the department or agency head

Serious or Continuing Noncompliance

The HHS regulations at 45 CFR 46.103(b)(5)(i) and the FDA regulations at 21 CFR 56.108(b)(2) require prompt reporting of *serious or continuing noncompliance* with the HHS or FDA regulations, or the requirements or determinations of the IRB/EC to the IRB/EC, appropriate institutional officials, the department or agency head², the OHRP and, when applicable, the FDA.

Suspension or Termination of IRB/EC Approval

The HHS regulations at 45 CFR 46.113 and the FDA regulations at 21 CFR 56.113 state that the IRB/EC has the authority to *suspend or terminate approval* of research that is not being conducted in accordance with the IRB's/EC's requirements or that has been associated with unexpected serious harm to subjects. These regulations mandate that when the reviewing IRB/EC suspends or terminates its approval of research, this information be reported to, among others, the investigator and sponsor. The IRB/EC action to suspend or terminate its approval is separate from any DAIDS action to wholly or partly suspend or terminate the current award³ for NIAID (DAIDS) -supported and/or -sponsored clinical research.

Research Misconduct

The Public Health Service (PHS) Policies on *research misconduct* at 42 CFR 93 mandate that institutions receiving PHS support for research activities, including NIAID (DAIDS)-supported and/or -sponsored clinical research, must comply with the instructions in this policy.

² DAIDS is serving on behalf of the department or agency head

³ 45 CFR 74.62(a)(3) and 45 CFR 92.43(a)(3)

II. Definitions

Adverse event (AE): Any untoward or unfavorable medical occurrence in a human subject⁴, 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.⁵ (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 noncompliance⁶: 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 increases the risk of harm to participants or others or has a significant adverse impact 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 DAIDS](#) 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)

⁴ The terms subject and participant are used interchangeably in this manual

⁵ [OHRP Guidance on Reviewing and Reporting Unanticipated Problems](#)

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

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 deviations.⁷ (DAIDS)

Reasonable Possibility: There is evidence to suggest a causal relationship between the research procedures and the adverse event, incident, experience, or outcome.⁸ (DAIDS)

Reporting Days: Those days that count toward the 3-day timeline provided for reporting of certain events to DAIDS. The criteria used to determine reporting days are as follows:

1. A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time
2. Monday through Friday count as reporting days
3. Saturday and Sunday are not considered reporting days
4. Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.
5. 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 the critical event 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. (DAIDS)

Research misconduct⁹: 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)

Research record: the record of data or results that embody the facts resulting from scientific inquiry, including but not limited to, research proposals, laboratory records, both physical and electronic, progress reports, abstracts, theses, oral presentations, internal reports, journal articles, and any documents and materials provided to HHS or an institutional official by a respondent in the course of the research misconduct proceeding. (ORI)

⁷Modified from the definition of protocol deviation in the 2008 FDA Compliance Program Guidance Manual bioresearch monitoring

⁸ Modified from FDA's definition at 21 CFR 312.32

⁹ 42 CFR 93.103

Serious noncompliance¹⁰: 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.¹¹ (DAIDS)

Suspension of IRB approval¹²: 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 approval¹³: 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 risks to subjects or others¹⁴: 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.¹⁵ (OHRP)

¹⁰45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(2)

¹¹ Modified from the Office of [Research Integrity's Responsible Conduct of Research glossary](#)

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

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

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

¹⁵ [OHRP Guidance on Reviewing and Reporting Unanticipated Problems](#)

III. Critical Events

For purposes of this manual, critical events include the following classes:

- A. Unanticipated Problems
- B. Serious or Continuing Noncompliance
- C. Suspension or Termination of IRB/EC Approval
- D. Suspected Research Misconduct

See Appendix A: [Examples of Critical Events](#).

The “Identification and Classification of Critical Events: DAIDS Responsibilities” policy directs DAIDS staff to the appropriate section(s) in this manual for specific events that have occurred. The “Identification and Classification of Critical Events: Site Responsibilities” policy directs investigators and site personnel to the appropriate section(s) in this manual for specific events that have occurred.

For purposes of this manual, the *DAIDS staff member* is a: Program Officer (PO), Medical Officer (MO), or Contracting Officer’s Representative (COR).

Prior to reporting the event to DAIDS, the Principal Investigator PI and/or designee will follow their institution’s procedures and gather supplemental information as needed. It is expected that the following information will be available for review by DAIDS staff:

1. protocol related documents (e.g., protocol number, site informed consent(s), current investigators brochure);
2. copies of applicable source documents, case report forms, or other materials that provide details about the incident;
3. any other available information that will help determine if a critical event has occurred.

Some critical events may lead to a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC) review. Determining when a DSMB or SMC review is needed is beyond the scope of this manual. See the DAIDS policy on Study Progress and Safety Monitoring for further information. The actions in this manual are in addition to any recommendations made by a DSMB or SMC.

A. Unanticipated Problems

DAIDS

The *DAIDS staff member* will inform his/her Program or Office Director and others as appropriate of the unanticipated problem (UP). See Appendix B: [Determining Which Adverse Events Are Unanticipated Problems](#).

- i. The DAIDS staff member will work in conjunction with other DAIDS staff, if needed, to:
 1. review the planned (corrective) action(s) associated with the UP for appropriateness and adequacy.
 2. determine if additional corrective actions need to be taken. (See Appendix C: [Examples of Corrective Actions](#).)
- ii. The DAIDS staff member will verify that corrective actions have been implemented.

When appropriate, the *supervisor* of the DAIDS staff member or designee will ensure the Network leadership or the grant or contract PI has been notified of the unanticipated problem.

The *DAIDS Program or Office Director or designee* will notify the Director of Office for Policy in Clinical Research Operations (OPCRO), and the Director of DAIDS as appropriate, of the UP.

Institution(s)

The *awardee institution* will ensure the NIAID Clinical Terms of Award and Terms of the Federalwide Assurance (FWA) for the Protection of Human Subjects are met.

- i. The awardee institution will ensure there is prompt reporting of the UP to their IRB/EC, appropriate institutional officials, the responsible DAIDS program officer (PO) or contracting officer's representative (COR)¹⁶, and applicable regulatory entities, including OHRP and FDA, when appropriate.
- ii. The awardee institution will assure that appropriate actions have been taken by all subawardees and that required reports have been sent to applicable regulatory entities.

The *subawardee institution* will ensure the Terms of the FWA for the Protection of Human Subjects are met.

¹⁶ From the Guidance for Complying with the NIAID Clinical Terms of Award

- i. The subawardee institution will ensure there is prompt reporting of the UP to the local IRB/EC and other institutional officials per its institutional policy.
- ii. The subawardee institution will inform the awardee institution of the UP and actions taken.

IRB/EC

- i. The *IRB/EC* will review reports of UPs involving risks to participants or others.
- ii. The IRB/EC will approve corrective actions per institutional policy and ensure that these actions are implemented to protect the rights and welfare of all participants and remediate the situation.

PI or designee

The *PI or designee* (e.g., Investigator of Record (IoR), Clinical Research Site (CRS) Leader) will notify DAIDS when an unanticipated problem (UP) involving risks to participants or others has occurred.

- i. The PI or designee will provide an initial report to the DAIDS PO, MO, or COR as soon as possible, but no later than three reporting days after he/she becomes aware of the UP.

The initial report can be done via oral or written communication. Oral communication will be followed up with written communication summarizing known facts. (See Appendix D: [Reporting Critical Events to DAIDS.](#))

- ii. The PI or designee will report the UP to the IRB/EC in accordance with institutional policies.
- iii. The PI or designee will determine if immediate suspension of some (e.g., suspend enrollment for new participants) or all research activities is warranted while the UP is being evaluated.
- iv. The PI or designee will follow the action(s) as directed by the IRB/EC, DAIDS, or other relevant entity.
- v. The PI or designee will provide timely updates to the appropriate DAIDS staff member on all follow-up reports and communications. The PI or designee will submit a follow-up or final report within 15 calendar days that he/she becomes aware of the event and continue to provide updates until

the CE issue is resolved. The report(s) will include all of the information related to the UP that is available at the time, including corrective actions and relevant IRB/EC correspondence.

B. Serious or Continuing Noncompliance

DAIDS

The *DAIDS PO, COR, or designee* will inform his/her Program or Office Director and others as appropriate of the serious or continuing noncompliance.

- i. The DAIDS PO, COR, or designee will work in conjunction with other DAIDS staff, if needed, to:
 1. review the planned (corrective) action(s) associated with the serious or continuing noncompliance for appropriateness and adequacy.
 2. determine if any additional corrective actions need to be taken. (See Appendix C: [Examples of Corrective Actions.](#))
- ii. The DAIDS PO, COR, or designee will verify that corrective actions have been implemented.

When appropriate, the *supervisor* of the DAIDS staff member or designee will ensure the Network leadership or the grant or contract PI has been notified of the serious or continuing noncompliance.

The *DAIDS Program or Office Director or designee* will notify the Director of Office for Policy in Clinical Research Operations (OPCRO), and the Director of DAIDS as appropriate, of the serious or continuing noncompliance.

DAIDS Independent Monitors

DAIDS Independent Monitors, including Clinical Site and Study Monitoring (CSSM) contractors and other clinical site monitors, will promptly report serious or continuing noncompliance to the DAIDS Program Officer or COR per their reporting guidelines.

Institution(s)

The *awardee institution* will ensure the NIAID Clinical Terms of Award and Terms of the Federalwide Assurance (FWA) for the Protection of Human Subjects are met.

- i. The awardee institution will ensure there is prompt reporting of the serious or continuing noncompliance to their IRB/EC, appropriate institutional officials, the responsible DAIDS PO or COR¹⁷, and applicable regulatory entities, including OHRP and FDA, when appropriate.

¹⁷ From the Guidance for Complying with the NIAID Clinical Terms of Award
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- ii. The awardee institution will assure that appropriate actions have been taken by all subawardees and that required reports have been sent to applicable regulatory entities.

The *subawardee institution* will ensure the Terms of the Federalwide Assurance (FWA) for the Protection of Human Subjects are met.

- i. The subawardee institution will ensure there is prompt reporting of the serious or continuing noncompliance to the local IRB/EC and other institutional officials per its institutional policy.
- ii. The subawardee institution will inform the awardee institution of the serious or continuing noncompliance and actions taken.

IRB/EC

- i. The *IRB/EC* will determine when serious or continuing noncompliance has occurred or review noncompliance reports from other entities.
- ii. The IRB/EC will approve corrective actions per institutional policy and ensure that these actions are implemented to protect the rights and welfare of all participants and remediate the situation.

PI or designee

The *PI or designee* (e.g., Investigator of Record (IoR), Clinical Research Site (CRS) Leader) will notify DAIDS when serious or continuing noncompliance has occurred.

- i. The PI or designee will provide an initial report to the DAIDS PO, COR, or designee as soon as possible, but no later than three reporting days after he/she becomes aware of the noncompliance.
- ii. The initial report can be done via oral or written communication. Oral communication will be followed up with written communication summarizing known facts. (See Appendix D: [Reporting Critical Events to DAIDS.](#))
- iii. The PI or designee will report the noncompliance to the IRB/EC in accordance with institutional policies.
- iv. The PI or designee will determine if immediate suspension of some (e.g., suspend enrollment for new participants) or all research activities is warranted while the noncompliance is being evaluated.

- v. The PI or designee will follow the action(s) as directed by the IRB/EC, DAIDS, or other relevant entity.
- vi. The PI or designee will provide timely updates to the DAIDS PO, COR, or designee on all follow-up reports and communications. The PI or designee will submit a follow-up or final report within 15 calendar days of becoming aware of the noncompliance and continue to provide updates until the CE issue is resolved. The report(s) will include all of the information related to the noncompliance that is available at the time, including corrective actions and relevant IRB/EC correspondence.

C. Suspension or Termination of IRB/EC Approval

DAIDS

The *DAIDS PO, COR, or designee* will inform his/her Program or Office Director, grants management specialist or contracting officer, and others as appropriate of the suspension or termination of IRB/EC approval.

- i. The DAIDS PO, COR, or designee will work in conjunction with other DAIDS staff to:
 1. review the planned (corrective) action(s) associated with the suspension or termination of IRB/EC approval for appropriateness and adequacy.
 2. determine if additional corrective actions need to be taken. (See Appendix C: [Examples of Corrective Actions](#).)
- ii. The DAIDS PO, COR, or designee will verify that corrective actions have been implemented.

The *supervisor* of the DAIDS staff member or designee will ensure the Network leadership or the grant or contract PI has been notified of the suspension or termination of IRB/EC approval.

The *DAIDS Program or Office Director or designee* will notify the Director of Office for Policy in Clinical Research Operations (OPCRO) and the Director of DAIDS of the suspension or termination of IRB/EC approval.

Institution(s)

The *awardee institution* will ensure the NIAID Clinical Terms of Award and Terms of the Federalwide Assurance (FWA) for the Protection of Human Subjects are met.

- i. The awardee institution will ensure there is prompt reporting of the suspension or termination of IRB/EC approval to appropriate institutional officials, the responsible DAIDS PO or COR, OHRP, and FDA (when applicable).¹⁸
- ii. The awardee institution will assure that appropriate actions have been taken by all subawardees and that required reports have been sent to applicable regulatory entities, including OHRP and FDA, when applicable.

¹⁸ From the Guidance for Complying with the NIAID Clinical Terms of Award

The *subawardee institution* will ensure the Terms of the Federalwide Assurance (FWA) for the Protection of Human Subjects are met.

- i. The subawardee institution will ensure there is prompt reporting of the suspension or termination of IRB/EC approval to the local IRB/EC and other institutional officials per its institutional policy.
- ii. The subawardee institution will inform the awardee institution of the suspension or termination of IRB/EC approval and actions taken.

IRB/EC

- i. The *IRB/EC* will promptly notify the investigator and institutional officials in writing of any suspension or termination of its approval, including the reason(s) for this action.¹⁹
- ii. The IRB/EC will approve corrective actions to ensure that the rights and welfare of all participants are protected and to remediate the situation.

PI or designee

The *PI or designee* (e.g., Investigator of Record (IoR), Clinical Research Site (CRS) Leader) will notify DAIDS as soon as possible, but no later than three reporting days after becoming aware of the suspension or termination of IRB/EC approval, through the DAIDS Protocol Registration System²⁰ (DPRS) if the IRB/EC suspends or terminates part or all of the research activities for the study.

- i. The PI or designee will notify the DAIDS PO or COR directly if the study is not registered through the DPRS. (See Appendix C: [Reporting Critical Events to DAIDS](#).)
- ii. The PI or designee will report the IRB/EC actions to the relevant protocol team and network leadership.
- iii. The PI or designee will forward a copy of all correspondence from the IRB/EC pertaining to the suspension or termination, including corrective actions.
- iv. The PI or designee will follow the action(s) as directed by the IRB/EC, DAIDS, or other relevant entity.
- v. The PI or designee will provide timely updates to DAIDS on all follow-up reports and communications.
- vi. In order to resume the research, the PI must receive written communication from both the IRB/EC that it has reapproved the study, and concurrence from DAIDS.

¹⁹ 45 CFR 46.113 and 21 CFR 56.113

²⁰ See the [Protocol Registration Manual](#) for further information

Responsible Party

When applicable, the *Responsible Party* will update the study record in ClinicalTrials.gov with the overall [recruitment status](#) and/or the location (facility) recruitment status of individual sites when IRB/EC approval has been suspended or terminated.

D. Suspected Research Misconduct

Awardee Institution

The *awardee institution* will investigate whether an allegation of fabrication, falsification, or plagiarism is research misconduct.

The awardee institution will coordinate the handling of research misconduct allegations originating at the subawardee's site.

The awardee institution will retain research misconduct records²¹ per Federal guidelines and regulations.²² See [DAIDS Policy on Storage and Retention of Clinical Research Records](#) for additional information²⁶.

DAIDS staff

NIAID has a [Standard Operating Procedure \(SOP\) on Research Misconduct](#) that describes NIAID staff actions (including DAIDS staff) after receiving allegations of research misconduct. The NIAID SOP does not address a site's actions and responsibilities associated with allegations of research misconduct.

DAIDS staff will treat all information regarding an allegation of research misconduct as strictly confidential.

- i. DAIDS Staff will not be involved in the determination or investigation of research misconduct. The DAIDS staff member that receives an allegation of research misconduct from a DAIDS monitor or other source will forward the report to his/her supervisor for further review and action.
- ii. The DAIDS staff member will work in conjunction with his/her supervisor and refer to the "DAIDS Policy on Identification and Classification of a Critical Event: DAIDS Responsibilities" to determine if the allegation of research misconduct represents an additional class of Critical Event.

The *supervisor* of the DAIDS staff member or designee will notify the Director of Office for Policy in Clinical Research Operations (OPCRO) or designee, and the Director of DAIDS as appropriate, of the research misconduct allegation and any other classes of critical event(s) that occurred.

- iii. The *Director of OPCRO or designee* will notify the NIAID Research Integrity Officer (RIO) of the research misconduct allegation.

²¹ Research misconduct records include records related to investigations of research misconduct and records of research misconduct proceedings

²²PHS 42 CRF 93.223 & 93.224

Site

Site staff, including site personnel and the PI and/or designee (e.g., Investigator of Record (IoR), Clinical Research Site (CRS) Leader), will follow the institution's policy, procedure, and process for reporting allegations of research misconduct, including protecting the confidentiality of the person(s) making an allegation of research misconduct, the person(s) against whom the allegation of research misconduct is directed, and the study participants.

- i. Site personnel will report allegations of research misconduct to the PI and/or designee within 24 hours of becoming aware of the incident.
- ii. In instances when 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 and DAIDS.
- iii. The *PI and/or designee* will notify the appropriate person within the institution (e.g., institution's Research Integrity Officer), the IRB/EC, and the appropriate DAIDS staff member of all applicable, known facts about the allegation.
- iv. The PI and/or designee will review the available information and assess whether the allegation of research misconduct represents an additional class of Critical Event. See the DAIDS policy on "Identification and Classification of a Critical Event: Site Responsibilities" for further information.
- v. The IRB/EC, PI and/or designee will determine if immediate suspension of some (e.g., suspend enrollment for new participants) or all research activities is warranted while the allegation is being evaluated.
- vi. The *institution's RIO and/or designee* will follow NIH and institutional policies when assessing the allegation to determine whether the allegation:
 1. meets the definition of research misconduct;
 2. involves PHS²³ supported research, research training, or research records; *and*
 3. is sufficiently credible and specific so that potential evidence of research misconduct may be identified²⁴.
- vii. The institution's RIO will ensure that the IRB/EC has been notified of the research misconduct allegation and any decision to open an investigation.

²³ All NIAID (DAIDS) supported and or sponsored research is also supported by PHS

²⁴ 42 CFR 93.307

The institution's RIO will also provide written notice to the HHS Office of Research Integrity (ORI) prior to beginning an investigation of the research misconduct.

- viii. The PI or designee will inform DAIDS of the institution's interim and final actions in response to the investigation of research misconduct allegations.

IV. References

[HHS regulations for the Protection of Human Subjects at 45 CFR 46](#)

[FDA regulations on Institutional Review Boards at 21 CFR 56](#)

[FDA regulations on Investigational New Drug Application at 21 CFR 312](#)

[PHS Policies on Research Misconduct at 42 CFR 93](#)

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

[OHRP Guidance on Reporting Incidents to OHRP, June 20, 2011](#)

[Terms of the Federalwide Assurance \(FWA\) for the Protection of Human Subjects](#)

[OHRP Guidance on IRB Continuing Review of Research](#)

[OHRP correspondence, September 29, 2008](#)

[FDA Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse event reporting to IRBs-Improving Human Subject Protection](#)

[FDA Guidance for Industry and Clinical Investigators: The use of clinical holds following clinical Investigator Misconduct](#)

[FDA draft Guidance for IRBs, Clinical Investigators, and Sponsors IRB Continuing Review after Clinical Investigation Approval, January 2012](#)

[FDA Compliance Program Guidance Manual, Bioresearch Monitoring Clinical Investigators and Sponsor-Investigators, Guidance for FDA Staff, December 9, 2008](#)

[ORI Responsible Conduct of Research \(RCR\) administrators glossary](#)

[ClinicalTrials.gov protocol registration system information](#)

[NIH Grants Policy Statement, Part II: Terms and Conditions of NIH Grant Awards](#)

[NIH Grant Policy Statement, Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General](#)

[NIH Grants Policy Statement, Part II: Terms and conditions of the NIH Grant award, Public Policy Requirements and Objectives, Research Misconduct](#)

[NIH Policies and Procedures for NIH Extramural Staff Handling Allegations of Research Misconduct](#)

[NIAID Clinical Terms of Award](#)

[NIAID Guidance for Complying with the NIAID Clinical Terms of Award](#)

[NIAID SOP Research Misconduct Cases](#)

DAIDS Policy on Identification and Classification of Critical Events: [DAIDS Responsibilities](#)

DAIDS policy on Identification and Classification of Critical Events: [Site Responsibilities](#)

[DAIDS policy on Storage and Retention of Clinical Research Records](#)

[DAIDS policy on Study Progress and Safety Monitoring](#)

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

[DAIDS Protocol Registration Manual](#)

Appendix A. Examples of Critical Events

Examples of *unanticipated problems* involving risks to participants or others may include but are not limited to:

- a. Loss of a computer that contains participants' private identifiable information
- b. Loss of study agent, resulting in a delay of administering study agent for an agent that holds out the prospect of providing a direct benefit to participant
- c. Participant experiences physical violence (e.g., domestic) as a result of participating in a clinical research study
- d. Inadvertent disclosure of family member's or partner's health status (e.g., Human Immunodeficiency Virus (HIV), tuberculosis (TB), or Hepatitis B positive), due to participation in the research
- e. Participant receives wrong study agent and does not experience any adverse effects. Note that receiving the wrong study agent is always an unanticipated problem, regardless of whether the participant experiences any adverse event.
- f. Participant is hospitalized for grade 4 pancreatitis that is unexpected and there is a reasonable possibility that the AE is related to participation in the research. Note that this incident meets the criteria of a Serious Adverse Event (SAE) and is reportable to DAIDS in an expedited timeframe.

Examples of *serious noncompliance* may include but are not limited to:

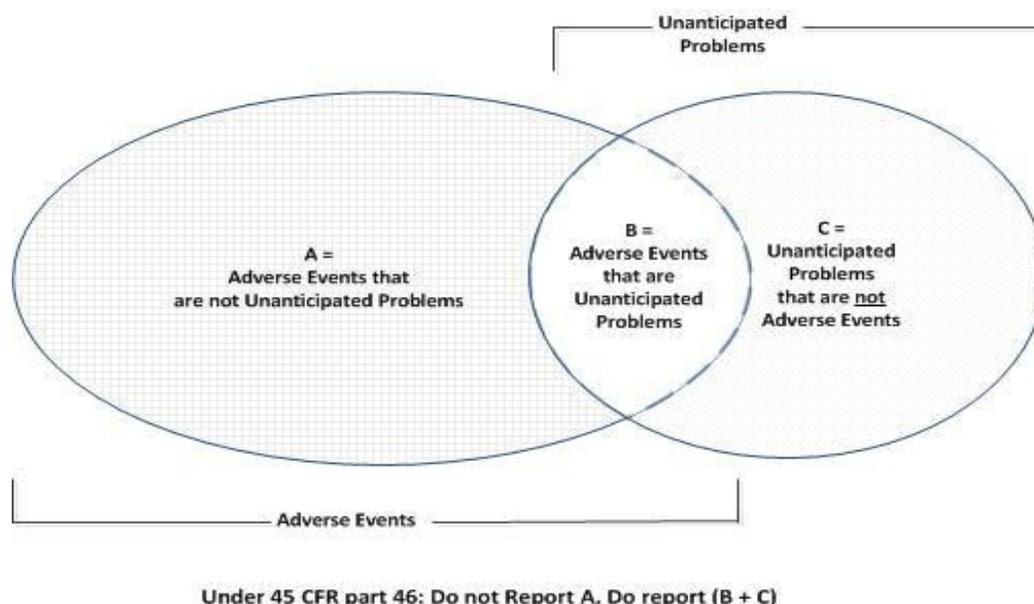
- a. Failure to obtain prospective, legally authorized informed consent
- b. Failure to conduct the research in accordance with the Institutional Review Board (IRB)/Ethics Committee (EC)-approved study
- c. Failure to obtain continuing review
- d. Failure to maintain accurate study records, submit required adverse event reports, report changes to the research, or report unanticipated problems posing risk to participants or others to the IRB/EC
- e. Screening procedures to assess participants eligibility performed before obtaining informed consent
- f. Participant enrolled in research during period of time when there was no current IRB/EC approval
- g. Participant enrolled in research for which the participant did not meet eligibility criteria, with possible serious health-related consequences to participation

Examples of *continuing noncompliance* include, but are not limited to:

- a. Consistently late submission of continuing review materials
- b. Consistently late submission of IRB/EC required adverse event and protocol deviation reports
- c. Consistently late submission of IRB/EC required progress reports
- d. Consistently uses expired version of informed consent document

Appendix B. Determining which Adverse Events are Unanticipated Problems²⁵

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



The diagram illustrates three key points:

1. The vast majority of adverse events occurring in human participants are not unanticipated problems.
2. A small proportion of adverse events are unanticipated problems.
3. Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events.

The key question regarding a particular adverse event is whether it meets the three criteria listed in the Unanticipated Problems definition and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

1. Is the adverse event unexpected?
2. Is there a reasonable possibility that the adverse event is related to participation in the research?
3. Does the adverse event suggest that the research places participants or others at a greater risk of harm than was previously known or recognized?

²⁵ Appendix B text modified from [OHRP's Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)

If the answer to **all three questions** is yes, then the adverse event is an unanticipated problem and must be reported to appropriate entities under the HHS regulations at 45 CFR 46. The next three sections discuss the assessment of these three questions.

A. Assessing whether an adverse event is unexpected

OHRP defines an *unexpected adverse event* as follows:

Any adverse event occurring in one or more persons participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

(1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol related documents, such as the IRB/EC-approved research protocol, any applicable investigator brochure, and the current IRB/EC-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; *or*

(2) the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event. (Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

It may be difficult to determine whether a particular adverse event is unexpected. Determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all participants enrolled in the research.

The vast majority of adverse events occurring in the context of research are *expected* in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of participants' underlying diseases, disorders, and conditions; and (3) participants' predisposing risk factor profiles for the adverse events. Thus, most individual adverse events do not meet the first criterion for an unanticipated problem and do not need to be reported under the HHS regulations at 45 CFR 46.

B. Assessing whether there is a reasonable possibility that an adverse event is related to participation in research

Adverse events may be caused by one or more of the following:

1. The *procedures* involved in the research;
2. An underlying disease, disorder, or condition of the participant; or
3. Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the participant.

In general, adverse events that are determined to be at least partially caused by the procedures involved in the research would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by the participants underlying disease, disorder, or condition or other circumstances unrelated to the research or participants underlying disease, disorder, or condition would be considered unrelated to participation in the research.

Reasonable Possibility is defined as follows:

There is evidence to suggest a causal relationship between the research procedures and the incident, experience, or outcome.

It may be difficult to determine whether there is a reasonable possibility that the adverse event is related to participation in the research. Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported under the HHS regulations at 45 CFR 46.

C. Assessing whether an adverse event suggests that the research places participants or others at a greater risk of harm than was previously known or recognized

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*.

A *serious adverse event* is any adverse event that:

- (1) results in death;
- (2) is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- (3) results in inpatient hospitalization or prolongation of existing hospitalization;
- (4) results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- (5) results in a congenital anomaly/birth defect; or
- (6) based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

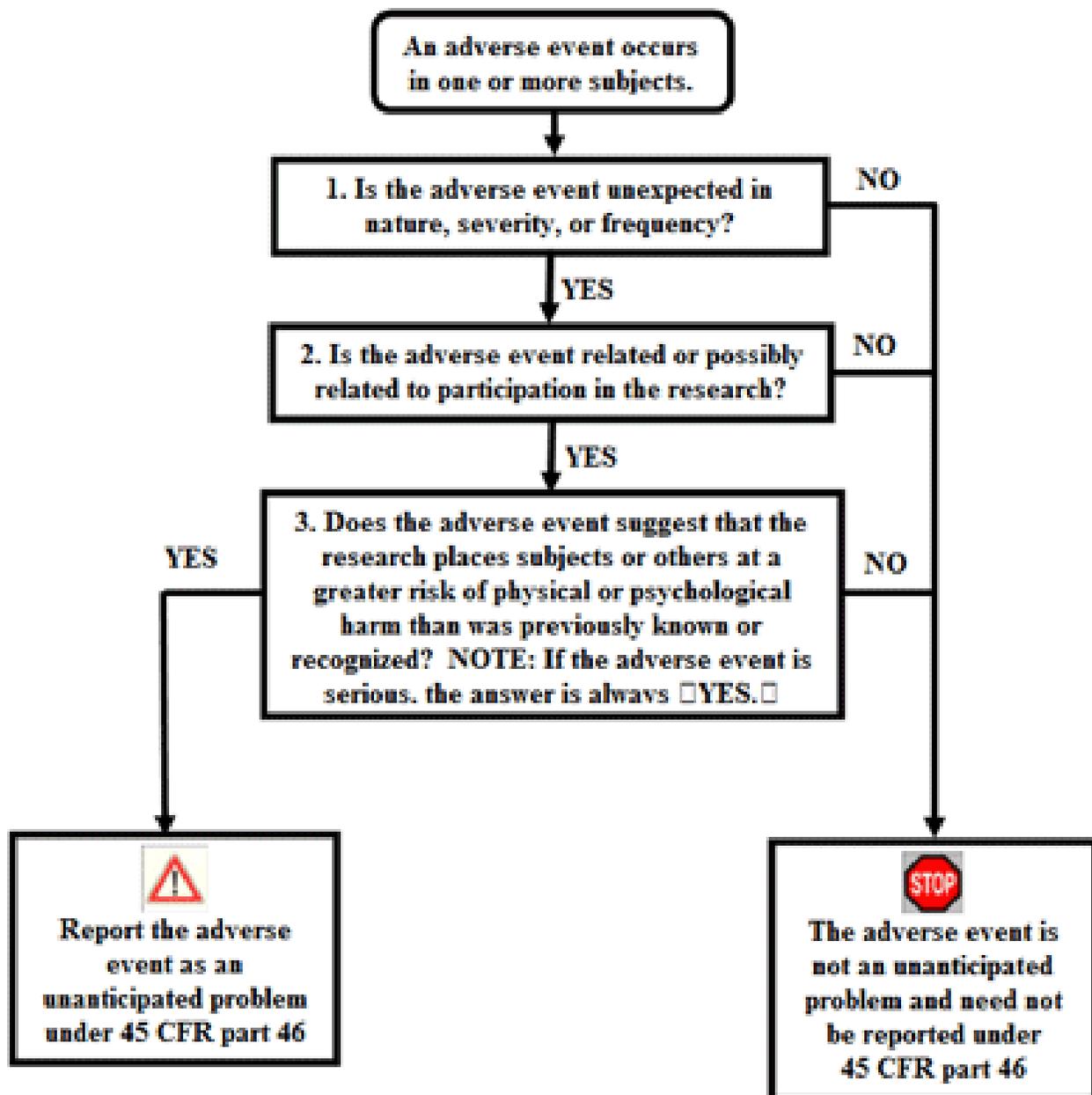
Adverse events that are unexpected, present a reasonable possibility that the adverse event is related to participation in research, and *serious* are the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants.

IRBs/ECs have authority to suspend or terminate approval of research that, among other things, has been associated with unexpected serious harm to participants (45 CFR 46.113). In order for IRBs/ECs to exercise this important authority in a timely manner, they must be informed promptly of those adverse events that are unexpected, present a reasonable possibility that the adverse event is related to participation in the research, and serious (45 CFR 46.103(b)(5)).

However, other adverse events that are unexpected and present a reasonable possibility that the adverse event is related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR 46.

Algorithm for Determining if an Adverse Event is an Unanticipated Problem



Appendix C. Examples of Corrective Actions

Examples of actions that may be taken in response to unanticipated problems involving risks to participants or others may include but are not limited to:

1. Implementing a protocol change to eliminate an apparent immediate hazard for participants before obtaining Institutional Review Board (IRB)/Ethics Committee (EC) approval or DAIDS concurrence.
2. Modifying the informed consent document(s) to include a description of newly recognized risk(s) and providing an information sheet about newly recognized risk(s) to previously enrolled participants.
3. Modifying the inclusion or exclusion criteria to mitigate the newly identified risks.
4. Implementing additional procedures to monitor the participant safety.
5. Suspending new participant enrollment or terminating the protocol and developing a plan to consider the well-being of currently enrolled participants.

Examples of actions that may be taken in response to serious or continuing noncompliance may include but are not limited to:

1. Informing current participants of information that may affect their willingness to continue in the research.
2. Designating a new PI who will assume responsibilities for the participants and carrying out the IRB/EC decision. (*note: this may require Program Officer and Grants Management approval*)
3. Requiring additional training or re-training for the PI and/or study team.
4. Increasing monitoring of the research by requiring the PI to submit special reports (e.g., adverse events or outcomes, quarterly progress reports, increasing frequency of continuing review) for ongoing research activities.
5. Suspending the grant.²⁶

Examples of actions that may be taken in response to suspension or termination of IRB/EC approval may include but are not limited to:

1. Notifying currently enrolled participants that the study has been suspended or terminated, including the rationale for such action and informing participants of any follow-up procedures permitted or required by the IRB/EC.
2. Withdrawing currently enrolled participants when withdrawal will not adversely affect their rights and welfare.
3. Allowing participants to continue on study (e.g., treatment with an investigational drug) if the IRB/EC determines that it is in their best interests.

²⁶ NIH Grant Policy Statement- Part II: Terms and Conditions of NIH Grant Award, [8.5.2 Suspension, Termination, and Withholding of Support](#)

4. Requiring the PI to submit a proposed procedure for management of participants on the study and special reports (e.g., adverse events or outcomes, increasing frequency of continuing review) concerning participants or requiring additional training or re-training for PI and/or study team.
5. Appointing a senior investigator as a mentor for current and/or future research activities until desired competence is achieved.

Appendix D. Reporting Critical Events to DAIDS

To fulfill the regulatory requirements for reporting certain critical events, the Division of AIDS (DAIDS) would consider it acceptable for an institution to comply with written procedures specifying that the following information be included in a report submitted to DAIDS:

For unanticipated problems involving risks to participants or others:

Name of the institution (e.g., university, hospital, foundation, school, etc.) conducting the research;

- a. Title of the research project and/or grant, contract or cooperative agreement in which the problem occurred;
- b. Name of the principal investigator (PI) on the protocol;
- c. Number of the research project assigned by the Institutional Review Board (IRB)/Ethics Board (EC) and the number of any applicable National Institute of Allergy and Infectious Diseases (NIAID) (DAIDS) award(s) (grant, contract, or cooperative agreement);
- d. A detailed description of the problem; and
- e. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend participant enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.).

For serious or continuing noncompliance:

- a. Name of the institution (e.g., university, hospital, foundation, school, etc.) conducting the research;
- b. Title of the research project and/or grant, contract or cooperative agreement in which the noncompliance occurred, or, for IRB/EC or institutional noncompliance, the IRB/EC or institution involved;
- c. Name of the PI on the protocol;
- d. Number of the research project assigned by the IRB/EC and the number of any applicable NIAID (DAIDS) award(s) (grant, contract, or cooperative agreement);
- e. A detailed description of the noncompliance; and
- f. Actions the institution is taking or plans to take to address the noncompliance (e.g., educate the investigator, educate all research staff, educate the IRB/EC or institutional official, develop or revise IRB/EC written procedures, suspend the protocol, suspend the investigator, conduct random audits of the investigator or all investigators, etc.).

For suspension or termination of IRB/EC approval:

- a. Name of the institution (e.g., university, hospital, foundation, school, etc.) conducting the research;
- b. Title of the research project and/or grant, contract or cooperative agreement that was suspended or terminated;
- c. Name of the PI on the protocol;

- d. Number of the research project assigned by the IRB/EC that was suspended or terminated and the number of any applicable NIAID (DAIDS) award(s) (grant, contract, or cooperative agreement);
- e. A detailed description of the reason for the suspension or termination; and
- f. The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.)