Adverse Event (AE), Unanticipated Problem (UP), And Serious Adverse Event (SAE) Reporting Policy

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This document outlines the NICHD policy for reporting AEs, UPs, and SAEs for all research activities and contracts funded in whole or in part by the institute.

Report SAEs to NICHD

AEs and UPs that need to be reported promptly to NICHD are termed "serious adverse events" or SAEs. Reportable SAEs are defined as those AEs and UPs that are serious, related to the research, and unexpected.

NICHD does not classify or adjudicate reportable AEs and UPs (i.e., SAEs) but recognizes the authority of relevant regulatory bodies (e.g., Institutional Review Boards [IRBs], Data and Safety Monitoring Boards [DSMBs], U.S. Food and Drug Administration [FDA], etc.) to determine the seriousness, relatedness, and unexpectedness of reportable events and to make determinations on study continuance.

NICHD is responsible for the oversight of reportable SAEs, and that oversight entails receipt of appropriate documentation from the Principal Investigator (PI) of SAE occurrences and follow-up decisions made by regulatory bodies. Documentation of the reportable SAEs and regulatory decisions must comply with the PI's written institutional procedures. The timeframe for submission of documentation to NICHD must also comply with the PI's written institutional procedures.

How to Comply with NICHD Policy

The award PI and authorized organizational representative (AOR)/signing official (SO) or investigational new drug (IND)/investigational device exemption (IDE) holder will submit the following:

- Before the project starts:
  - NICHD requires that the institution's written reporting timeframe (e.g., within 1 week of the investigator becoming aware of the SAE) be clearly specified in the study Data and Safety Monitoring Plan.
  - If there is no plan, investigators should follow their IRB guidance. Guidance and suggestions to assist IRBs in defining "prompt" reporting is available from the HHS Office for Human Research Protections website.
  - NICHD also requires that the designated reporting official (i.e., PI, AOR, or sponsor or the IND/ IDE holder) for the study be noted in the Data and Safety Monitoring Plan.

- If an SAE occurs after the project starts:
  - **Documentation of the SAE.** NICHD must receive this documentation within the same timeframe required by an institution's written reporting procedures outlined in the Data and Safety Monitoring Plan.
    - The documentation submitted to NICHD can be the same as the prepared report submitted to the IRB, DSMB, FDA, or another designee. The documentation submitted to NICHD should not contain any personal identifiers for participants.
    - Documentation should be emailed to NICHDAdverseEventRep@mail.nih.gov, with the subject line "Serious Adverse Event Notification" followed by the PI's name and grant/contract number.
  - Prompt notification of adjudication decisions. NICHD requires prompt notification of decision from the IRB, DSMB, FDA, or other designees, such as:
    - Serious or continuing non-compliance determinations
    - Suspensions or terminations of research
  - **When requested by NICHD, prompt follow-up documentation.** This documentation can include additional details about the event or information that became available after the initial SAE was reported. If follow-up documentation is required by an institution's written reporting procedures to the IRB, the DSMB, FDA, and other designees, NICHD may request it.

Questions regarding this policy and procedure can be sent to NICHDAdverseEventRep@mail.nih.gov.

Regulatory Background

According to 45 CFR 46 and Office of Human Subjects Research Protections (OHRP) guidance documents pertaining to all non-exempt human-subjects research, the highest-priority AEs generally meet three criteria for "prompt" or "expedited" reporting to NICHD: expectedness, relatedness, and riskiness. Riskiness refers to foreseeable risks and anticipated benefits to participating in research (45 CFR 46.111(a)(2)).

Various factors are taken into consideration when assessing the nature, likelihood, and acceptability of the risks of harm.

- **Minimal Risk** to subjects means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests and that confidentiality is adequately protected.

- **Greater-than-Minimal Risk** to subjects means that the probability and magnitude of harm or discomfort anticipated in the research risks are more than minimal risk, but not significantly greater.

- **Significantly Greater-than-Minimal Risk** to subjects means that there is a probability of an event that is serious, prolonged, and/or permanent occurring as a result of study participation or there is significant uncertainty about the nature or likelihood of adverse events. Trials with Significantly Greater than Minimal Risk require adequate protections for foreseeable adverse events.

For further information on risk monitoring, see guidance from the National Institute of Mental Health that NICHD also follows.

NICHD's oversight applies to clinical trials authorized under FDA regulations (21 CFR 50, 56, 312, 812). These rules dictate the timeline and process for reporting by PIs or sponsors (i.e., IND holders) directly to the FDA.

FDA rules on reporting safety events differ based on whether the clinical trial is FDA-authorized as a clinical investigation of a drug or medical device (e.g., IND or IDE) or the trial is lawfully conducted without an IND or IDE but includes administration or use of FDA-regulated products (i.e., lawfully marketed drugs or medical devices). FDA guidance describes when drug studies may be conducted without an IND and the process for requesting an IND waiver. Consult Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies.

Resources

UPs Involving Risks & AEs Guidance (2007): https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#AA

Guidance on Reporting Incidents: https://www.hhs.gov/ohrp/compliance-and-reporting/guidance-on-reporting-incident/index.html

AE Reporting to IRBs: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/institutional-issues/institutional-review-board-written-procedures/index.html

Improving Human Subjects Protection: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection

Definitions

Adverse event (AE): Any untoward or unfavorable medical occurrence in a human subject, 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

- **External AE:** From the perspective of one particular institution engaged in a multicenter clinical trial, external AEs are those experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.
- **Internal AE:** From the perspective of one particular institution engaged in a multicenter clinical trial, internal AEs are those experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all AEs would be considered internal AEs.

Possibly related to the research: There is a reasonable possibility that the AE, incident, experience, or outcome may have been caused by the procedures involved in the research (modified from the definition of "associated with use of the drug" in FDA regulations at 21 CFR 312.32(a)).

Serious adverse event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject'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).)

Unanticipated problem (UP) involving risks to subjects or others: Any incident, experience, or outcome that meets ***all*** the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to a subject's participation in the research
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized

Unexpected AE: Any AE occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- 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-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject'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).)

Non-compliance: Failure of investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not. Visit https://www.hhs.gov/ohrp/compliance-and-reporting/evaluating-institutions/index.html for more information.

Protocol deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol. For more information, visit https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-c/index.html.

Reminders

Definitions of all expected non-serious AEs and SAEs (e.g., anaphylaxis to a drug) that are related to an investigational medical product or behavioral intervention must be pre-specified in the protocol and informed consent, or Investigator's Brochure (as required by FDA).

The research reporting official who will report SAEs to NICHD should be designated in the Data Safety Monitoring Plan (i.e., the PI, AOR, or Sponsors/IND or IDE holders).