NIA Adverse Event and Serious Adverse Event Guidelines

BACKGROUND

This guideline describes the requirements and processes for reporting adverse events and unanticipated problems to the National Institute on Aging (NIA). It incorporates guidelines provided by the Office of Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) and describes Food and Drug Administration (FDA) reporting requirements. NIH is obligated to ensure that researchers comply with their approved reporting procedures. Clinical trial investigators funded by NIA are obligated under federal regulations to appropriately inform the Institute of adverse events and unanticipated problems, and NIA is required to ensure that the appropriate procedures are in place to support this reporting.

DEFINITIONS

Definitions are from the January 2007 OHRP *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, OHRP Guidance*.

Adverse Event (AE):

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Serious Adverse Event (SAE):

Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Unanticipated Problem (UP):

Defined by DHHS 45 CFR part 46 as any incident, experience, or outcome that meets all of 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 study population;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Events versus Unanticipated Problems

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

RESPONSIBILITIES

Both the NIA and the investigators it funds have responsibilities with respect to safety reporting.

Investigators

Investigators conducting clinical research are responsible for:

- Assurance that their protocols are conducted in compliance with these guidelines.
- Submission of IRB-approved protocol to the NIA program office and to the Data and Safety Monitoring Board (DSMB), as applicable.

  A Data and Safety Monitoring Plan (DSMP) that is commensurate with the study risk and reflects this guideline should also be submitted either as part of the application or a separate document.

  - The DSMP should describe collection and reporting plans for adverse events, serious adverse events, and unanticipated problems commensurate with nature and complexity of the study.
  - The DSMP should include recipients of Serious Adverse Event and Unanticipated Problem reports (e.g. Institutional Review Boards (IRBs), DSMB or Safety Officer, and NIA).

The DSMB should approve both the protocol and the DSMP.

- Adherence to the DSMP with respect to timely submission of adverse events, serious adverse events, and unanticipated problems.

NIA

NIA program staff members are responsible for providing:

- Assistance to extramural investigators in understanding and applying adverse event and serious adverse event guidelines and for ensuring compliance with OHRP guidance in all NIA funded clinical research.
- Oversight of these guidelines, which includes periodic review and revision as relevant rules and regulations change.
- Assurance that the DSMP addresses reporting of adverse events, serious adverse events, and unanticipated problems.
- Verification that all corrective action plans have been adequately implemented.
- Assurance that the study has an independent safety monitoring body commensurate with study risk (DSMB or Safety Officer).
- Ongoing oversight of the safety reporting process to assure that potential safety issues are addressed.

REPORTING PROCESSES

Adverse Events, Serious Adverse Events, and Unanticipated Problems have specific reporting procedures.

Adverse Event Reporting

All AEs are collected on an Adverse Event Form, either in paper or electronic format. A sample AE Form is shown in Adverse Event Form. All AEs experienced by the participant during the time frame specified in the protocol (e.g., from the start of intervention through the end of the study) are to be reported, as outlined in the protocol. The reporting requirements to the IRB, to the NIA and to the FDA (in case of drug and device studies) may differ and must be complied with.

Please note that the AE form contains a column to indicate whether the event is SERIOUS. Thus, SAEs are a subset of the reported AEs.

Routine reporting of AEs is described in the DSMP and may be monthly or quarterly as determined with the NIA staff and /or the DSMB/Safety Officer.

Serious Adverse Event Reporting

When SAEs occur that are unanticipated (i.e., not listed in the Data and Safety Monitoring Plan) and that are related to the intervention, they should be reported to NIA

Program Officer and to the DSMB Chair (or a Safety Officer, for studies without the DSMB) or to the designated DSMB member if a DSMB is established within 48 hours of study's knowledge of SAE. The summary of all other SAEs should be reported to NIA Program Officer and to the DSMB (or a Safety Officer) quarterly, unless otherwise requested by the DSMB or a Safety Officer. Expected SAEs should be listed in the Data and Safety Monitoring Plan. All deaths require expedited reporting (usually within 24 hours of study's knowledge of death). The report of death should be submitted to NIA Program Officer and to the DSMB Chair (or a Safety Officer, for studies without the DSMB) or to the designated DSMB member if a DSMB is established.

The expedited report should be followed by a detailed, written SAE report as soon as possible. Follow up information may be required and asked for by the independent safety monitoring body directly, or through the NIA or its representative. A sample of the SAE reporting form used for NIH Intramural Programs is shown in Serious Adverse Event Form.

Unanticipated Problem Reporting

Investigator institutions must have written procedures for ensuring prompt reporting to the IRB and NIA, and others as appropriate, of any Unanticipated Problem involving risks to study participants or others (45 CFR 46.103(b)(5)). The Unanticipated Problems reporting procedures must include a corrective plan and measures to prevent reoccurrence. It is recommended that such events be reported within 48 hours to NIA unless they are also SAEs.

Reports of Unanticipated Problems, as defined above, should be forwarded to OHRP using ohrp@osophs.dhhs.gov, typically within two weeks of the event.

The flow chart in AE/SAE Process Flow provides an algorithm of the reporting process.

CLASSIFYING ADVERSE EVENTS

Adequate review, assessment, and monitoring of adverse events require that they be classified as to ***severity***, ***expectedness***, and potential ***relatedness*** to the study intervention. Study protocols must include a description of how adverse events will be classified in these terms. These classifications determine the reporting requirements.

Severity

Classifications often include the following:

- ***Mild:*** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate:*** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by

simple therapeutic measures; moderate experiences may cause some interference with functioning

- ***Severe:*** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Severity is not synonymous with seriousness. A ***severe*** rash is not likely to be an ***SAE.*** Likewise, a ***severe*** headache is not necessarily an ***SAE.*** However, ***mild*** chest pain may result in a day's hospitalization and thus is an ***SAE.***

Expectedness

AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label. Categories are:

- ***Unexpected*** **-** nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.

- ***Expected*** **-** event is known to be associated with the intervention or condition under study.

Relatedness

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

- *Definitely Related*: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- *Possibly Related:* An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- *Not Related:* The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

SAFETY REPORTING REQUIREMENTS FOR STUDIES INVOLVING INVESTIGATIONAL NEW DRUGS (IND)

The FDA amended its regulations governing IND safety reporting for human drug products (21 CFR 312 and 320). The following modified definitions and reporting requirements apply to research subject to IND applications:

Definitions:

Sponsor:

Sponsor means a person or institution that takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a Sponsor-Investigator.

Sponsor-Investigator:

Sponsor-Investigator is an individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed. The requirements applicable to Sponsor-Investigator include both those applicable to an investigator and a sponsor.

Adverse event:

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Adverse reaction:

Any adverse event caused by the drug.

Suspected adverse reaction:

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

***Serious* adverse event or *serious* suspected adverse reaction:**

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization, or prolonged of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious, when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

***Life-threatening* adverse event or *life-threatening* suspected adverse reaction:**

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

***Unexpected* adverse event or *unexpected* suspected adverse reaction:**

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure (IB); is not listed at the specificity or severity that has been observed; or if IB is not required or not available, is not consistent with the risk information described in the protocol or safety monitoring plan.

IND Safety Reporting

An overview of the Safety Reporting requirements are described below and in the flow diagram, as shown in Figure 1.

Fatal or life-threatening serious unexpected suspected adverse reactions (SUSARs) reports:

The sponsor (or sponsor-investigator) must notify the FDA of any SUSARs to the study drug as soon as possible but *no later than 7 calendar days* after the initial receipt of the information.

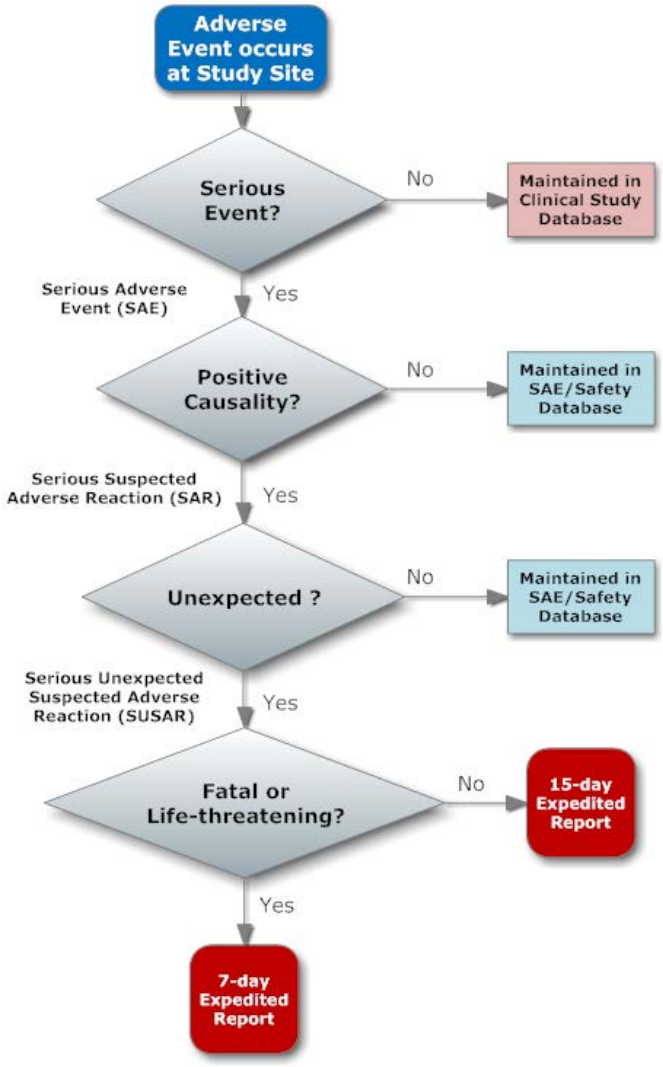
Other reporting requirements:

The sponsor (or sponsor-investigator) must also notify the FDA and all participating Principal Investigators (in multi-site studies) in an IND safety report about potential serious risks, from clinical trials and any other source, *no later than 15 days* in the following cases:

- **SUSARs that are not fatal or life-threatening**. Any suspected adverse reaction that is *both serious and unexpected* must be reported. The report must proceed only if there is evidence to suggest a causal relationship between the drug and the adverse event.
- **Finding from other studies**. Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under serious and unexpected adverse reactions above) must be reported whether or not conducted under an IND or whether or not conducted by the investigator, that suggest a significant risk in humans exposed to the drug.
- **Findings from animal or in vitro testing**. Any finding from animal or in vitro testing whether or not conducted by the investigator that suggest a significant risk in humans exposed to the drug such as reports of mutagenicity, teratogenicity, or carcinogenesis or reports of organ toxicity, must be reported.
- **Increased rate of occurrence of serious suspected adverse reactions.** Any clinically important increase in the rate of serious suspected adverse reactions over that listed in the protocol or IB must also be reported.
- **SUSARs that are part of study endpoints.** Study endpoints (e.g. mortality or major morbidity) must be reported to the FDA as described in the protocol and ordinarily would not be reported as IND safety reports. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under 21 CFR 312.32 as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

Note: The most frequent and most serious adverse experiences that are not serious unexpected suspected adverse reactions to the study drug have to be summarized and reported to the FDA in the annual IND report.

Figure 1: FDA IND Expedited Safety Reporting Requirements for Individual Case Safety Reports Flow



Investigator Reports:

An investigator (if he/she is not a sponsor-investigator) must report to the sponsor any *serious* adverse event within 24 hours of investigator learning about the event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

The investigator must also record *nonserious* adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

References

NIA Implementation of Policies for Human Intervention Studies

January 2007 OHRP Guidance *on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events,* http://www.hhs.gov/ohrp/policy/advevntguid.html

21 CFR 312.50, General Responsibilities of the Sponsor, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.50

21 CFR 312.32, IND Safety Reports, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

ICH E6 5.0 Sponsor, Good Clinical Practices, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf