AMGA Guidelines for Reporting Adverse Events and Unanticipated Problems Involving Risks to Research Subjects or Others

Federal regulations [45 CFR Part 46] require institutions conducting non-exempt research funded by or conducted through the Department of Health and Human Services (HHS) to establish written procedures to promptly report adverse events and unanticipated problems involving risks to human subjects or others.

These guidelines apply to all non-exempt research studies conducted by any investigator(s) and/or organization(s) acting on behalf of AMGA receiving funding from an HHS agency, including the National Institutes of Health (NIH). All investigators involved in non-exempt human subjects' research on behalf of AMGA are obligated to comply with these reporting requirements.

DEFINITIONS

Adverse Event (AE)

Any untoward or unfavorable medical occurrence in a human study subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, associated with subject's involvement in the research study. This includes any such event occurring within the timeframe of the study (as specified within the research protocol) whether the event is directly related or not 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
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition that investigators judge to represent significant hazard

Unanticipated Problem (UP)

An unanticipated problem is 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 approved IRB protocol-related documents (e.g., research protocol and informed consent documents); and (b) the characteristics of the study population;

- Related or possibly related to participation in the research; "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; and

- Suggests 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.

CLASSIFYING ADVERSE EVENTS

Adverse events are classified according to their severity, expectedness, and potential relatedness to the study intervention. Study protocols will include a description of how adverse events will be classified for non-exempt research studies using the following classifications.

Severity

Classifications 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 usually improve with 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; and they are usually incapacitating.

Severity is not the same as "seriousness." A *severe* rash or headache in most cases is not likely to be considered an SAE. However, mild chest pain that could result in a day's hospitalization would be considered an SAE.

Expectedness

An assessment must also be made to determine whether an AE is expected or unexpected (e.g. not anticipated based on current knowledge in the protocol, investigator brochure, etc.):

- **Unexpected**: Nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, or other study documents.

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

Relatedness

Site Investigators are responsible for assessing the relationship of each event to the study intervention/subject's participation using a comprehensive scale to categorize the event:

- **Definitely Related**: Clearly related to the intervention/procedure
  - Follows a reasonable time sequence from administration of the study intervention/procedure
  - Follows a known or expected response pattern to the suspected intervention/procedure
  - Is confirmed by improvement on stopping and reappears on repeated exposure
  - Cannot be reasonably explained by known characteristics of the subject's clinical status.

- **Possibly Related**: Could be related to the intervention/procedure
  - Follows a reasonable time sequence from administration of the study intervention/procedure
  - Follows a known or expected response pattern to the suspected intervention/procedure
  - Could readily have been produced by a number of other factors

- **Not Related**: Is clearly not related to the intervention/procedure
  - Another cause of the event is most plausible and/or
  - A clinically plausible sequence is inconsistent with the onset of the event
  - Study intervention and/or a causal relationship is considered biologically implausible

RESPONSIBILITIES

All Investigators participating in AMGA research funded by an HHS agency including NIH have responsibilities with respect to safety reporting.

Principal Investigators

The Principal Investigator (PI) is responsible for ensuring all study site personnel (including sub-investigators and other staff members) adhere to protocols and guidelines during and after study completion. Specifically, items for which the PI is responsible also include:

- Ensuring research protocols are conducted in compliance with federal regulations.

- Submitting an Institutional Review Board (IRB)-approved protocol to the appropriate program office and, when applicable, to the Data and Safety Monitoring Board (DSMB).

  Developing a **Data and Safety Monitoring Plan** (DSMP) commensurate with the level of anticipated study risk and submitting it with the application or separately. A DSMP is an individualized plan for the study written by the PI. The DSMP establishes mechanisms for review and evaluation of adverse and unanticipated study events and addresses other study data protection and safety issues. (See hyperlink above for more details.)

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

Site Investigators/Study Team Members

AMGA Site Investigators and research study teams will receive training on how to recognize and report adverse events and unanticipated problems. Each Site Investigator or member of the study team will be responsible for ensuring timely reporting of adverse events or unanticipated problems to the AMGA PI.
The process of recognizing, collecting, and reporting required data for these occurrences will be included in the research protocol and DSMP. This process will be described and explained to all team members with access to study subjects.

REPORTING PROCESSES

Adverse Event Reporting

All AEs will be described and collected using an **Adverse Event Form** and submitted in an encrypted, electronic format to the PI at AMGA. (See hyperlink for example of the NIH Adverse Event Form). Reporting forms may differ depending on a variety of factors (e.g., IRBs, the HHS Office of Human Research Protections (OHRP), or other institutional officials, safety monitoring bodies, and regulatory agencies may have different reporting requirements).

All AEs during the timeframe of the study experienced by subjects and described within the protocol (e.g., from the start of the intervention through the end of the study) must be reported. Routine reporting of AEs will be described in the DSMP and protocol documents. However, some AEs will be **serious**. Serious Adverse Events (SAEs) are a subset of reported AEs.

Serious Adverse Event Reporting

When unanticipated SAEs occur (i.e., not listed in the DSMP or protocol) and are related to the study intervention, these must be reported by the AMGA PI to the appropriate HHS Program Officer and DSMB Chair or designated DSMB member (or other safety monitoring body and/or officials) within 48 hours of discovery of the SAE.

Site Investigators and/or team members who discover potential SAEs must report them to the AMGA PI as soon as possible by email or telephone, but no later than 24 hours following discovery. Serious adverse events discovered by the clinical team should be presented to the AMGA PI, the site Investigator, and the study team, who together, with available data, will make a determination as to whether the event is unrelated, possibly related, or probably related to the study intervention or procedure (see categorizing on "relatedness" below).

The Site Investigator is also obligated to pursue and obtain additional follow-up information as requested by AMGA, the independent safety monitoring body, and the HHS institute or agency or its representative. If a serious adverse event occurs, the Site Investigator and/or a study team member must:

- **Notify AMGA PI immediately** by email or telephone.
- Obtain and maintain all pertinent records and materials related to the subject and the event, as well as all follow-up information.
- Complete the appropriate Adverse Event Form and send it via encrypted email **no later than 24 hours following discovery of the event**.
- **In the case of death, AMGA should be notified immediately** upon discovery.
- All information about AE and SAE events should be recorded using the appropriate Adverse Event Form and sent to:

    Elizabeth Ciemins, Ph.D., M.P.H., M.A.
    Vice President, Research and Analytics, AMGA
    Email: eciemins@amga.org, Phone: 406.281.3275

All deaths require expedited reporting (within 24 hours of the study team's knowledge). The Site Investigator and or a member of the site study team must inform the AMGA PI of the death of a subject immediately by telephone or email. The PI will submit an expedited report of death to the safety monitoring body, the HHS institute, or agency Program Officer immediately upon review of the report. After an expedited report has been submitted, a detailed, written SAE report must also be submitted.

Non-Serious Adverse Event Reporting

The Site Investigator or a member of the study team will report all non-serious adverse events to the PI **no later than 48 hours after discovery**.

A list of expected SAEs will be included in the Data and Safety Monitoring Plan. Routine reporting of all AEs are generally required on a monthly or quarterly basis unless otherwise instructed by safety officials. The AMGA PI

will submit a summary of all AEs (including SAEs and Unanticipated Problems) to the HHS Program and/or Safety Officer and the safety monitoring body in compliance with the reporting schedule.

Unanticipated Problem Reporting

AMGA must also report unanticipated problems to the IRB, the HHS Office of Human Research Protections (OHRP), and as appropriate to institutional officials and regulatory agencies. Unanticipated problems include any incident, experience, or outcome that is unexpected and is related or possibly related to the research intervention/procedure that could place subjects or others at a greater risk of harm (see definition above).

Only a small subset of AEs that occur will meet these criteria. Discovery of an unanticipated problem will usually require changes to the research protocol, informed consent processes, or other protocol documents. Corrective action may also be required to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes in response to an unanticipated problem include:

- Suspension of enrollment of new subjects
- Suspension of research procedures in enrolled subjects
- Modification of informed consent documents to describe newly recognized risks
- Provision of additional information about newly recognized risks to enrolled subjects
- Changes to the research protocol to eliminate apparent immediate hazards to subjects
- Modification of inclusion or exclusion criteria to mitigate newly identified risks
- Implementation of additional procedures for monitoring subjects

Other unanticipated problems that can occur involve social or economic harm rather than physical or psychological harm associated with AEs. Unanticipated problems can also place others who are not subjects at increased risk of harm. (For more information see: Examples of Unanticipated Problems That Do Not Involve Adverse Events and Need to Be Reported under the HHS Regulations at 45 CFR Part 46.)

AMGA has a master service agreement with the WCG IRB, an independent institutional review board providing ethical review for research studies involving human participants. WCG IRB is registered with the Office for Human Research Protections (OHRP and FDA) as IRB00000533 and will be the official IRB of record for all AMGA-sponsored, non-exempt research involving human participants. For protocols approved by the WCG IRB, reporting requirements are defined in the **WCG Policy HRP-071**.

Site Investigator or a member of the site study team must report Unanticipated Problems to the AMGA PI within 72 hours of knowledge of the event. The PI will notify the IRB, the HHS Office of Human Research Protections (OPRS), and as appropriate institutional officials and regulatory agencies and develop a plan for corrective action within two (2) weeks of discovery of the problem.

For more information:

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eciemins@amga.org 406.281.3275

References

HHS regulations for the protection of human subjects in research at 45 CFR 46. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

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

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

Glossary of Key Terms

Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported under the HHS Regulations at 45 CFR Part 46