

Clinical Trial Safety Assessment and Reporting

Introduction and Purpose

Assessment of safety events and accurate reporting of these events is critical to the conduct of a clinical study and ensures the safety of research participants.

The purpose of this SOP is to describe the collection, evaluation, documentation and reporting requirements for safety events such as Adverse Events (AE), Serious Adverse Events (SAE), Unanticipated Problems (UP), and other safety events that occur during the course of a clinical trial.

The Principal Investigator (PI) is responsible for overall conduct of the trial, protecting the rights, safety, and welfare of study subjects, and ensuring that an investigation is conducted in accordance with the protocol, Good Clinical Practice (GCP), Institutional Review Board (IRB), Food and Drug Administration (FDA) and all other applicable regulations.

Safety events should be collected and reported according to the protocol and the requirements described in this SOP, as applicable.

Definitions

Adverse Event (AE): An adverse event is any untoward medical occurrence (or worsening of an existing condition) in a clinical trial participant, which may or may not have a causal relationship with the study treatment.

Suspected adverse reaction: Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly/birth defect
6. Other serious important medical events

Unanticipated adverse device effect (UADE): Any serious adverse effect on health or safety of a participant or any life-threatening problem or death caused by, or associated with a device previously not identified in the investigational plan or

Clinical Trial Safety Assessment and Reporting

application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Safety Event Evaluation Criteria

Safety events must be evaluated by criteria that are relevant to the study protocol and applicable oversight agencies, and then reported within specific timelines. The study sponsor and applicable oversight agencies may have varying parameters for the evaluation criteria and reporting timelines. Additionally, the reviewing IRB for the study is likely to have specific evaluation criteria and reporting timelines.

Common governmental agencies with specific safety event evaluation criteria and reporting timelines include:

- DHHS Office of Human Research Protections (OHRP):
<https://www.hhs.gov/ohrp/compliance-and-reporting/guidance-on-reporting-incident/index.html>
- Food and Drug Administration (FDA):
 - For IND Trials - <https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports>
 - For IDE trials - <https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-reports>
- Department of Veterans Affairs:
VHA Directive 1058.01: <https://www.va.gov/oro/oropubs.asp>
- Department of Defense (DoD) Instruction 3216.02:
<https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/321602p.pdf>

The following general evaluation criteria are most commonly used.

Severity: Severity of an adverse event is determined after the designation of an adverse event. It refers to the intensity of the adverse event and its effect on the participant's health and wellbeing. Investigators may be asked to categorize the severity on a scale, such as the CTCAE scale that includes: Mild, Moderate, Severe, Life-threatening, Death. Please refer to section 2.2 for additional information on assessing severity.

Attribution or Relatedness: Also referred to as causality, or relationship to the research intervention. Attribution is the investigator's determination of whether there is a causal relationship between an adverse event and the IP or intervention. Given that it may be difficult to make a definitive attribution for some events, investigators may be asked to rate the likelihood of a causal relationship on a scale, such as Unrelated, Unlikely Related, Possibly Related, Probably Related, Definitely Related.

Clinical Trial Safety Assessment and Reporting

Expectedness: Refers to whether the adverse event and its nature, severity, and/or frequency is anticipated according to the current understanding of the research intervention (as described in the IRB approved protocol, investigator's brochure, informed consent document, and/or other relevant sources of information, such as product labeling and package insert) or the expected natural progress of any underlying disease or condition of the participants.

Prompt Reporting: Refers to the urgent, expeditious reporting that is required for events that meet certain criteria. Such reporting may be required by the reviewing IRB, the institution's Human Research Protection Program, the study sponsor, and applicable oversight agencies.

Acronyms

CFR:	Code of Federal Regulations
CRF:	Case Report Form
CRO:	Contract Research Organization
DLT:	Dose Limiting Toxicity
GCP:	Good Clinical Practice
HIPAA:	Health Insurance Portability and Accountability Act
ICH:	International Council on Harmonization
IDE:	Investigational Device Exemption
IDS:	Investigational Drug Services
IND:	Investigational New Drug
IP:	Investigational Product
IRB:	Institutional Review Board
PI:	Principal Investigator
SIM:	Study Initiation Meeting
SIV:	Site Initiation Visit
SOP:	Standard Operating Procedure
UP:	Unanticipated Problem
HRPP:	Human Research Protections Program

Clinical Trial Safety Assessment and Reporting

Procedure

1. Collection of Safety Events

- 1.1. The PI and all delegated study staff will review the following at the start of a study and for the duration of the study to maintain familiarity with the safety profile of the investigational product, as applicable:
 - Study protocol
 - Informed consent documents
 - Investigator's Brochure
 - Package insert or product labeling
 - Safety reports pertinent to the IP
 - Safety event evaluation criteria required by the reviewing IRB, the institution's Human Research Protection Program, the study sponsor, and applicable oversight agencies.
- 1.2. The study protocol will generally include a reporting window for adverse event collection that should be followed. If the protocol does not include a safety reporting window, all adverse events will be collected from commencement of the intervention phase until one of the following occurs:
 - 1.2.1 Safety follow-up window per protocol since last dose of IP or research intervention as defined by the protocol
 - 1.2.2 The participant's withdrawal of consent from the trial
 - 1.2.3 Safety events determined to be related to the IP or research intervention should be followed until resolution or stabilization
- 1.3. Prior to any clinical research intervention, the PI and delegated study staff will conduct a review of the participant's baseline conditions and comorbidities. This may include a review of the participant's systems including an assessment of medical history.
- 1.4. Throughout the conduct of the clinical trial, safety information will continue to be collected by the PI and delegated study staff and may come from a variety of sources, including but not limited to the following:
 - Direct report by the participant, spouse, caregiver etc. including participant completed diaries and questionnaires.
 - Observations made by an investigator during study procedures such as physical exams, performance status assessment, collection of vital signs, and administration of the research intervention

Clinical Trial Safety Assessment and Reporting

- Abnormal laboratory, EKG, and imaging (e.g., CT, MRI, PET/CT, X-rays, Ultrasound) findings that are determined to be clinically significant by the investigator
- Reports from non-study related medical encounters such as emergency department visits, hospital stays, primary care physician and other health care services

2. Evaluation of Safety Events

- 2.1. Once an adverse event has been identified, the severity, attribution, expectedness, outcome and seriousness of the event are assessed by the PI or a qualified delegated study team member, such as a sub-investigator. Research Coordinators should not evaluate safety events for these elements.
- 2.2. Severity is generally assessed according to the reviewing IRB's policy, the institution's HRPP policies, the study sponsor's policies and applicable oversight agencies. However, protocols may specify different scales or may require AEs to be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE). In these cases, protocol specifications should be adhered to and the CTCAE version number specified in the protocol should be used. It is possible that multiple scales may need to be used to assess severity of an event based on the policies and oversight of the study.
- 2.3. Attribution is generally assessed according to the reviewing IRB's policy, the institution's HRPP policies, the study sponsor's policies and applicable oversight agencies. However, individual protocols should be reviewed for additional instructions.
 - 2.3.1 If a study involves multiple medications or interventions, attribution should be assessed for each medication or intervention independently, unless the protocol specifies otherwise.
- 2.4. Adverse events should be assessed as expected or unexpected to the IP and/or study intervention based on the safety information found in the package insert for marketed drugs, investigator brochure, study protocol, informed consent forms and/or product labeling, as available. The natural progression of any underlying diseases or conditions the subject may have should also be considered when making this assessment.
- 2.5. Adverse Events are considered "Serious" if they result in the outcomes listed under the Serious Adverse Events (SAE) criteria of the Definitions and Acronyms section of this SOP. The protocol should be reviewed for additional events and outcomes that may be deemed "Serious" for the study.

Clinical Trial Safety Assessment and Reporting

- 2.6. The study protocol may also require an investigator or delegated team member to assess whether an adverse event meets the protocol-defined stopping rules such as criteria of a Dose Limiting Toxicity (DLT). The study team should pay special attention to stopping rules and DLTs to ensure the treatment/intervention assignment is safe prior to escalating to the next dose or level.
- 2.7. All laboratory and imaging reports should be reviewed by the investigator, or delegated team member, and any abnormal or out of range results assessed for clinical significance.

3. Documentation of Safety Events

- 3.1. For each study participant, adverse events should be cumulatively recorded and documented. For example, an adverse event log(s) in study source may be used to document adverse events. Alternatively, adverse event information may be recorded in source documents within participant records. For example, physician notes. Adverse events should be accurately transcribed in the study specific Case Report Forms (CRFs).
- 3.2. A template adverse event log can be found using the following link:
<https://qualitycompliance.research.utah.edu/toolkit.php>
- 3.3. The investigator or delegated team member should document his/her assessment of each adverse event on the log or in participant source documents. The assessment should include severity, attribution, expectedness, seriousness, and if the event meets criteria for a DLT.
- 3.4. Each adverse event recorded on the log or in source documents should be signed and dated by the investigator or designee.

4. Reporting Safety Events

- 4.1. Safety information must be reported to the Sponsor, CRO when applicable, IRB, Data Safety Monitoring Committee/Board, FDA, or other sponsoring agency as required by the protocol.
 - 4.1.1 The method of reporting may vary by study and is generally outlined in the protocol or a separate guidance document provided to the study team. Common methods of reporting include paper-based forms (such as MedWatch form FDA 3500A), Electronic Data Capture (EDC) system entry, or a separate reporting format.
 - 4.1.2 The extent and frequency of the reporting requirements depends on the expectedness, relatedness, and seriousness of the event.

Clinical Trial Safety Assessment and Reporting

- 4.1.3 If the protocol doesn't specify a timeframe for reporting SAEs, expedited reporting to the study sponsor or CRO is standardly required for participants who have received at least one dose of the study intervention. A standard reporting timeframe for initial SAE notification is 24 business hours from the investigator's first knowledge of the event.
 - 4.1.4 If the PI is unavailable, a Sub-Investigator can make the initial SAE assessment and submit in place of the PI. However, the PI always retains oversight.
 - 4.1.5 If the initial SAE report is missing information, a detailed follow-up report should be reported according to the protocol specified timeframes. If no timeframe is provided in the protocol, the follow-up information should be submitted promptly when new information is received.
- 4.2. Institutional Review Board (IRB) Reporting
- 4.2.1 The study team should refer to the IRB of record for guidance on reporting safety information including unanticipated problems or events.
 - 4.2.2 The PI or qualified designee will review and confirm the safety events meeting IRB reporting requirements.
 - 4.2.2.1 The University of Utah IRB requires adverse events to be reported if all three of the following criteria are met:
 - Unexpected
 - Definitely or probably related to the research
 - Places participants or others at greater risk of harm than previously known as a result of the event
- Refer to the following website for detailed information on this reporting process, including reporting timeframes:
- <https://irb.utah.edu/submit-application/forms/adverse-events.php>.
- 4.2.2.2 The study team will compile all necessary safety information for the submission of the event through the IRB's reporting mechanism. The PI or qualified designee will review and submit the final report to the IRB.
 - 4.2.2.3 All other adverse events and relevant safety information that occur or are collected during the course of the study will be summarized and reported to the IRB through the Continuing Review process.

Clinical Trial Safety Assessment and Reporting

4.2.3 For external Institutional Review Board studies where the University of Utah IRB is not the reviewing IRB, refer to the reviewing IRB's website and/or lead site as described in the protocol.

4.2.3.1 The University of Utah HRPP also requires reporting if the event impacted a local participant. Please refer the University of Utah IRB website above for reporting requirements.

4.3. Food and Drug Administration (FDA) Reporting

4.3.1 For studies that fall under FDA regulations, adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:

- Serious
- Unexpected
- Related (Definitely, probably, or possibly)

4.3.2 Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.

4.3.3 All other events that meet the criteria above will be reported within 15 calendar days of first knowledge of the event by the investigator.

4.3.4 For studies that are industry-sponsored or overseen by coordinating centers, the sponsor or coordinating center is responsible for submitting safety reports from the study to the FDA.

4.3.5 For Investigator-Initiated Studies (IITs), the Principal Investigator is responsible for reporting safety events to the FDA. Some departments may offer qualified support staff to sponsor-investigators to ensure safety reporting is done timely and accurately throughout the course of a study. In such cases, sponsor-investigators should utilize these services.

4.3.5.1 The Clinical Research Support Office (CRSO) at the University of Utah assists sponsor-investigators with all aspects of IND and IDE studies that include safety reporting. Sponsor-investigators within departments that do not have support services should contact the CRSO IND Specialist. Please refer to the following SOPs for complete details on IND and IDE services offered:

- IND studies:
https://qualitycompliance.research.utah.edu/resources/documents/uusop/uusop-11_idn-applications_03mar2021.pdf

Clinical Trial Safety Assessment and Reporting

- IDE studies:
https://qualitycompliance.research.utah.edu/resources/documents/uusop/uusop-12_ide-applications_03mar2021.pdf

4.3.5.2 The Research Compliance Office (RCO) at Huntsman Cancer Institute, University of Utah, assists sponsor-investigators with IND and IDE submissions for cancer related clinical trials. Please contact the HCI-RCO@utah.edu for assistance.

5. Reporting External Safety Events

- 5.1 External adverse events are safety events that occurs at institutions other than the University of Utah. For studies that are industry-sponsored or overseen by coordinating centers, the PI may receive safety reports from the sponsor or coordinating center. Examples include IND safety reports, external adverse event reports, Dear Investigator Letters, MedWatch forms, Council for International Organizations of Medical Sciences (CIOMS) and Serious Unanticipated Suspected Adverse Reaction (SUSAR) reports.
- 5.1.1 Study sponsors, coordinating centers and IP manufacturers may periodically submit safety reports and updates to the IB.
- 5.1.2 For all externally sponsored trials, the University of Utah expects sponsors to directly notify Investigators of important safety information and unanticipated problems that has implications for the conduct of the research (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150).
- 5.1.3 University of Utah investigators are not required to check Industry, CRO, or third-party web portals for possible new information in the absence of a notification (e.g., email).
- 5.1.4 External safety reports that do not have a clear indication of important safety information or an unanticipated problem classification will not be reported to the IRB. Such reports are not required to be acknowledged, signed, printed, or retained for the study file.
- 5.1.5 It is the sponsor's responsibility to provide an explanation of why an event was determined to be an unanticipated problem and clearly indicate the implications for the conduct of the study (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150). Sponsors must provide sufficient information to support a substantive review by investigators and the IRB for any event that results in changes to study conduct, informed consent document, or investigator brochure.

Clinical Trial Safety Assessment and Reporting

5.1.6 When the investigator is made aware of a potential UP from the sponsor, the study team has 10 business days to report the UP promptly to the University of Utah IRB. Please refer to the following website for detailed reporting requirements:

<https://irb.utah.edu/submit-application/forms/problems.php>

5.2 For IITs, where the investigator is also the sponsor, the sponsor-investigator is responsible for reviewing all safety data, notifying, and distributing reportable events to each participating investigator/site. Please refer to section 4.3.5.1 of this SOP for assistance available for sponsor-investigator initiated IND/IDE trials.

Materials Required

- Study protocol
- IRB of record safety event reporting requirements
- Template adverse event log:

<https://qualitycompliance.research.utah.edu/toolkit.php>

References

- University of Utah IRB:
<https://irb.utah.edu/submit-application/forms/adverse-events.php>
- 21 CFR Part 312.32 IND Safety Reporting:
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32>
- 21 CFR Part 812 Investigational Device Exemptions:
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=812>
- FDA Guidance for Industry: Safety Reporting Requirements for INDs and BA/BE Studies:
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-reporting-requirements-inds-investigational-new-drug-applications-and-babe>
- ICH Guidance for Industry E2: Clinical Safety Data Management:
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2a-clinical-safety-data-management-definitions-and-standards-expedited-reporting>
- NCI Common Terminology Criteria for Adverse Events:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Clinical Trial Safety Assessment and Reporting

Document Approval



6/24/2022

Erin Rothwell, Ph.D.
Interim Vice President for Research, University of Utah

DATE

Revision History

Version Date	Change Summary
29/Nov/2021	Original Version
2/Jun/2022	Adding investigator review and assessment of laboratory and imaging results

Printed or photocopied versions are considered unofficial copies unless it is the original signed document.