SERIOUS ADVERSE EVENTS

Introduction

Timely reporting of Serious Adverse Events (SAEs) is required by regulations of the Food and Drug Administration (FDA) and the National Cancer Institute (NCI). Such reporting is not merely a legal requirement, but a necessity for safe patient care and scientific communication by allowing the rapid dissemination of significant new findings to the investigators studying a drug.

What is an Adverse Event

An Adverse Event (AE) is defined by the FDA and by NCI in NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs, as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite).

An AE may consist of the following:

1) A new event which was not pre-existing at initial study drug administration.

2) A pre-existing event which recurs with increased intensity or increased frequency subsequent to study drug administration.

3) An event which is present at the time of study drug administration which is exacerbated following initial study drug administration.

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses. When an AE meets criteria for expedited reporting as an SAE, it must be reported only once unless the grade becomes more severe in the same or subsequent cycle/course.

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course. Once reported, a recurring AE requires expedited reporting if the grade increases from the grade originally reported or if hospitalization is associated with the recurrence.

A Serious Adverse Event (SAE) is defined by FDA and NCI as any adverse drug event (experience) occurring at any dose that in the opinion of either the investigator or sponsor results in any of the following outcomes:

1) Death

2) Life-threatening adverse drug experience

3) Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
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4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5) Congenital anomaly/birth defect

6) Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Although the precise reporting requirements vary, these definitions apply in general to investigational agents, commercial agents, or a combination of investigational and commercial agents. It is important to remember that all SAEs are adverse events, but not all adverse events are SAEs, and need to be expeditiously reported only if they meet the guidelines for expedited reporting in Section 16 of the protocol.

General SAE Reporting Policy

A Serious Adverse Event report must be submitted on any event which meets the reporting criteria specified in the relevant protocol (Section 16 or Section 8). These criteria vary depending on factors such as whether an investigational new drug (IND) has been given, the grade of the adverse event, whether or not the event resulted in hospitalization/prolongation of hospitalization, whether the event is expected or unexpected, and/or the attribution of the event to protocol treatment. If unclear about whether or not a particular event meets expedited reporting criteria, contact the SWOG SAE Program by email at adr@swog.org or by phone at 210-614-8808.

Adverse Events meeting the criteria for expedited reporting will be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

The reporting of SAEs is in addition to, not a substitute for, adequately reporting adverse events on study data records and in the final results of the clinical trial. All adverse events that rise to the level of an SAE should be clearly documented on study data forms in addition to submission of SAE reports.

Adverse Events determined to be reportable to the Institutional Review Board (IRB) responsible for oversight of the patient must be reported according to local policy and procedures. Documentation of IRB notification must be available for inspection during an audit.

Secondary Malignancy (a cancer caused by treatment for a previous malignancy and is NOT considered a metastasis of the initial malignancy) such as Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), and Myelodysplastic Syndrome (MDS) that occur in patients who are or have been on NCI protocols should be reported as SAEs via CTEP-AERS, as per reporting instructions in Section 16 (or Section 8) of the protocol.

Second Malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). For most protocols Second Malignancies require ONLY
routine reporting on the appropriate form in Medidata RAVE, however, in some protocols expedited reporting of Second Malignancies will also be required, this will be indicated in Section 16.1 (or Section 8).

**Pregnancy Reporting** should be done in an expedited manner for study participants who become pregnant while on study. In addition, pregnancy outcome including pregnancy loss and neonatal death will also be reported in an expedited manner. These events should be reported per instructions in Section 16 (or Section 8) of the protocol. A Pregnancy Report Form will also be completed and submitted per instructions on the form. The Pregnancy Report form is available at [http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm](http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm)

**Reporting an Adverse Event in an Expedited Manner - Points to Consider**

Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents. When a study utilizes a combination of investigational and commercial agents it will be important to determine if the administration of study agents is concurrent or sequential.

- **Concurrent administration** – when an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

- **Sequential administration** – when a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration, all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines of the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Utilize the current active version of NCI Common Terminology Criteria for Adverse Events (CTCAE); grade the adverse event(s). The CTCAE provides descriptive terminology and grading scale for each adverse event listed. Adverse events will be graded from 1 (mild) to 5 (fatal). A **copy of the CTCAE can be downloaded from the CTEP homepage. Additionally, if assistance is needed, the NCI has an index to the CTCAE that provides help for classifying and locating terms.**

Determine if the adverse event(s) resulted in hospitalization or a prolongation of hospitalization (> 24 hours).

Attribution may also play a role in determining whether or not an event meets expedited reporting criteria. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite; indicating whether or not there was a causal relationship between the study treatment agent and the event that occurred. This decision is based on knowledge of drug, time relationship between the event and study drug administration, patient’s health history/pre-existing conditions, and/or concomitant medications. Each individual study agent must be assigned an attribution (or relationship) to the event reported. Your Investigator should be the one to make this assignment.
In determining if an adverse event meets expedited reporting criteria for some protocols you may have to determine if the adverse event is Expected, Unexpected, or an Exception to Expedited Reporting. Refer to Section 3.0 and/or Section 16.1 (or Section 8) of the protocol.

Late Effect: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions in the appropriate table in Section 16 of the protocol.

Reporting SAEs for SWOG Studies

The general criteria for SAE reporting are as specified in the NCI Division of Cancer Treatment publication, NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs. However, because reporting guidelines frequently vary based on specific study requirements, Section 16 (or Section 8) of the protocol should always be consulted for applicable reporting instructions. When a site becomes aware of an adverse event that meets expedited reporting criteria, a CTEP-AERS report should be initiated within 24 hours and submission of a complete report within the number of days specified in the protocol. Adverse events are to be coded and graded according to the adverse event criteria version specified in the protocol. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting.

The CTEP Active Version of the CTCAE is identified and located on the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

All current active studies use CTCAE v5.0 for SAE reporting although some studies will continue to use Version 4.0 for routine adverse event reporting.

1) Death that cannot be classified with a more specific CTCAE grade 5 adverse event should be reported as Death, NOS.

2) Surgical and medical procedures should not be reported as SAEs or adverse events unless explicitly so directed in a protocol. However, adverse events may result from a surgical or medical procedure, if this occurs then the event(s) should be reviewed.

Supporting Documentation

For SAEs reported on patients who have received an investigational drug given under an Investigational New Drug (IND) application held by SWOG and for Grade 5 events on Non-SWOG held IND studies, the following must be submitted to SWOG Operations Office within 5 calendar days: A copy of the first page of the printed CTEP-AERS report along with copies of relevant clinical and/or protocol data sufficient to document the SAE and substantiate the investigator’s attribution of the adverse event(s) being reported. Supporting data which will be submitted will
also be indicated in the “Additional Information” section of the CTEP-AERS report. Autopsy reports should be submitted when available.

The SWOG SAE Coordinator will send a reminder email when supporting documentation is to be submitted to the SWOG Operations Office. If the documentation does not arrive by the due date, or if required elements are missing, you will be sent a follow-up notice with a short extension of the submission deadline. If an adequate response to the follow-up request is not received within one week, the institution's Principal Investigator will receive a formal letter from the Group Chairman requesting the required data. If there is not then a prompt response, disciplinary action will be recommended.

When submitting supporting documentation the following information should be legibly printed, typed or written on each page submitted: Protocol Number, SWOG Patient ID Number, and CTEP-AERS Ticket Number.

Amending a CTEP-AERS Report

Once an original CTEP-AERS report has been submitted, any changes or additions to the original information will be made by creating an amendment to that report. You should create an amendment to the original CTEP-AERS report when additional events occur during that same cycle/course as indicated on the original report, if there is a worsening of the reported event(s), to report additional follow-up information, correct information, and/or in response to a query.

Note: All events that occur and are associated with a single course/cycle/reporting period should be reported under a single ticket number, amending as needed. This applies even if the patient has been taken off protocol treatment as you are still associating the event to the last course/cycle on which study agent(s) were last administered.

RAVE / CTEP-AERS Integration

Recently activated protocols are now utilizing Medidata Rave / CTEP-AERS integration for SAE reporting. Adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. All protocols utilizing the Medidata Rave/CTEP-AERS integration will have additional instructions in Section 16.1 (or Section 8) to guide you.

Submitting a CTEP-AERS Report

When a CTEP-AERS report is created it can remain “pending” in the CTEP-AERS System for 10 calendar days (5 calendar days if the report is initiated using the 24-hour notification pathway). During this time the report is accessible to the site to make additions, revisions, or to withdraw. If the report is not submitted within the appropriated timeframe, the CTEP-AERS System will flag the report as “initiated, not submitted” and the report will be dropped from the system. Once this occurs the report will no longer be accessible and a new report will have to be created to report the event(s).
Once the site submits a CTEP-AERS report, that report is considered “submitted to the Group”. The SWOG SAE Coordinator now has access to the report for review and can make revisions to the report and even withdraw the report on behalf of the submitting site (the site will not be able to access the report during this review). During the time that the SAE Coordinator is reviewing the CTEP-AERS report it continues to be “pending” and the 10 calendar day (5 calendar day for reports initiated using the 24-hour notification pathway) countdown continues until the SWOG SAE Coordinator completes the submission. Once this review is done the SAE Coordinator completes the submission. The “pending” countdown to removal from the CTEP-AERS System stops and the site can once again access the report.

**Evaluation of SAEs**

For NCI-held IND studies and commercial drug studies, evaluations of SAEs will be done by the SWOG SAE Coordinator as CTEP-AERS reports are received. A minimal review will be conducted to ensure all reported events meet the criteria outlined in Section 16 (or Section 8) of the protocol and that all mandatory sections of the report are complete. If a previous CTEP-AERS report was submitted for the same cycle of treatment, the site will be informed that the current report will be withdrawn and the previous report must be amended to include the new SAE.

For SWOG-held IND studies and Grade 5 events, as described above, for NCI-held IND studies and commercial drug studies, additional supporting documentation is always required on submitted SAEs. An evaluation by the SWOG Physician Reviewer will be completed on receipt of the required supporting documentation.

The Physician Reviewer evaluates the report, the supporting documentation, and the reporting investigator’s description of the event, adverse event code(s), grade(s), expectedness, and attribution(s). If the initial evaluation of a report suggests that a protocol violation may be implicated in the adverse event(s) being reported, the report and supporting documentation will be reviewed for protocol compliance by the SAE Coordinator.

Based on the Physician Reviewer’s assessment he/she may recommend changes in SAE code(s), grade(s), and attribution(s). If the Physician Reviewer recommends changes in SAE code(s), grade(s), or expectedness, these recommendations will be provided to the submitting investigator, giving him/her the opportunity to challenge any changes. The Physician Reviewer’s recommendations may also be sent to the Study Chair for comment. If no challenge to the recommended changes is received within 7 calendar days, the judgment of the Physician Reviewer will be reflected in the entries made in the SWOG database.

If the Physician Reviewer recommends a change in SAE attribution that would shift the event from being related (definitely, probably or possibly) to not related (unlikely, unrelated) category or from an unrelated to a related category, these recommendations will be provided to the submitting investigator with an urgent request for response. The recommendations may also be sent to the Study Chair for comment. If the submitting investigator does not respond in agreement with the change in attribution, or provide rationale on why the attribution should not be changed, within 7 calendar days, the Executive Officer will be asked to adjudicate the attribution. The Executive Officer may elect to consult with the Study Chair and others, as needed to make a determination. No changes in attribution will be made in the SWOG database unless either 1) the investigator agrees with the change; or 2) the Executive Officer agrees with the change. No change in the
investigator’s attribution will be considered if the change does not shift the SAE from a related to an unrelated category, or from an unrelated to a related category.

Non-Compliance and Determination of Disciplinary Action

Group institutions will be reviewed routinely and during Quality Assurance Audits to determine adherence to the requirement for reporting SAEs and submitting reports within the appropriate number of days as outlined in the protocol. Institutions found to have repeated or significant delays in reporting during the review period will be required to submit a written plan for preventing such occurrences in the future.

If there are repeated delays in SAE reporting or if a protocol violation was involved in a reported SAE disciplinary action may result. Disciplinary action can include suspension of registration and/or conduct of a for cause Quality Assurance Audit at the option of the Group Chair.
DEFINITIONS

Adverse Event – is defined by the FDA and by NCI as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite).

Attribution – is an assessment of the relationship between the AE and the medical intervention. Attributions are one of the following: Unrelated (the AE is clearly NOT related to the intervention), Unlikely (the AE is doubtfully related to the intervention), Possible (the AE may be related to the intervention), Probable (the AE is likely related to the intervention), and Definite (the AE is clearly related to the intervention).

Commercial Agents – are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

Concurrent Administration – can occur when an investigational agent(s) is used in combination with a commercial agent(s), when this is the case the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Expected Events – are those that have been previously identified as resulting from administration of the agent.

Hospitalization – is defined, for expedited reporting purposes, as an inpatient admission equal to or greater than 24 hours.

Institutional Review Board – is any board, committee, or other group formally designated by an institution to review biomedical research involving human subjects, and to approve the initiation, and conduct of periodic review of such research.

Investigational Agent – is a protocol drug administered under an Investigational New Drug (IND) submission. In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) – provides a descriptive terminology that is to be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

Sequential Administration – can occur when a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration. All expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the
patient begins receiving the commercial agent(s) the all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

**Serious Adverse Event** – is defined by FDA and NCI as any adverse drug event (experience) occurring at any dose that in the opinion of either the investigator or sponsor results in any of the following outcomes: death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization (> 24 hours), a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, or an Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon 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.

**Specific Protocol Exceptions to Expedited Reporting (SPEER)** – is a subset of AEs within the CAEPR that contains a list of events that are protocol-specific exceptions to expedited reporting. AEs listed on the SPEER should be reported expeditiously via CTEP-AERS only if they exceed the grade of the event listed in the parenthesis after the event.

**Unexpected Event** – is an adverse event, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the protocol, consent form, or drug package insert.
SAE Resources/Support

SWOG Homepage www.swog.org

CTEP http://ctep.cancer.gov

NCI Guidelines for Investigators: Adverse Event Reporting Requirement for DCTD (CTEP and CIP) and DCP INDs and IDEs Effective September 16, 2013

CTEP-AERS
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

FDA http://www.fda.gov

Contact the SWOG SAE Program
General email: adr@swog.org
Phone: 210-614-8808

CTEP-AERS Medical Questions/Help
Email: aemd@tech-res.com
Phone: 301-897-7497

CTEP-AERS Technical Questions/Help
Email: ncitelphelp@ctep.nci.nih.gov
Phone: 1-888-283-7457

References:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs Effective September 16, 2013

SWOG Policy #23 – Serious Adverse Events