

SWOG
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Departments Affected: All

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SERIOUS ADVERSE EVENTS

Introduction

The timely reporting of serious adverse events is required by the Food and Drug Administration (FDA) (Ref. Title 21, Code of Federal Regulations, Part 312). Such reporting is necessary for both patient safety and scientific communication by allowing the FDA and National Cancer Institute (NCI) to rapidly disseminate new findings to investigators studying the drug.

Definition of an Adverse Event (AE)

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

Definition of a Serious Adverse Event (SAE)

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: death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization (for >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.

Although the precise reporting requirements vary, these definitions apply in general to investigational agents, commercial agents, or combinations of investigational and commercial agents.

The definition of an SAE does include myelosuppression with a drug known to cause that adverse event if it is clearly the major factor leading to a death. All SAEs are adverse events, but not all adverse events are SAEs, and need to be reported only if they meet the guidelines for expedited reporting in Section 16 of the protocol.

Reporting Serious Adverse Events

Investigators are required to submit an SAE report on any event which meets the reporting criteria specified in the relevant protocol. These criteria vary depending on factors such as whether an investigational new drug (IND) is involved. SAEs on protocols not coordinated by SWOG should normally be reported directly to the cooperative group that coordinates the study according to the protocol guidelines, and a copy of the report is provided to the SAE Program staff in the Operations Office via the CTEP-AERS system. An investigator who is unclear whether or to whom to report a particular event should contact the SAE Coordinator in the Operations Office at 210-614-8808 or adr@swog.org for assistance.

The reporting of SAEs is in addition to, and does not supplant, the necessity of adequately reporting adverse events on the data records and in the final results of the clinical trial. All SAEs should be clearly documented on study data forms in addition to submission of SAE reports.

NOTE: All SAEs must also be reported to the local Institutional Review Board (IRB) per institutional guidelines. Documentation of IRB notification must be available for inspection during an audit.

Reporting Serious Adverse Events 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 of the protocol should always be referenced for applicable reporting instructions. 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 Common Terminology Criteria for Adverse Events (CTCAE) will be used in reporting SAEs on a given protocol. All current active studies use CTCAE version 5.0 for SAE reporting although some studies will continue to use Version 4.0 for routine adverse event reporting.

Guidance for reporting surgical and medical procedures:

"Surgical and medical procedures" should be not be reported as SAEs or adverse events unless explicitly so directed in a protocol.

"Surgical and medical procedures," "falls," and "infusion site extravasation" should not be reported in an expedited manner as SAEs unless clearly associated with other reportable SAEs.

Guidance for reporting a death for a patient on protocol treatment or within the timeframe after the last administration of study agent(s) as indicated in the SAE reporting criteria in section 16.1:

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

Death that is instantaneous or within one hour of onset of symptoms or an unobserved cessation of life that cannot be attributed to a specific CTCAE term should be reported as Sudden Death NOS.

Death due to disease progression will be reported using the CTCAE (v5.0) term Disease Progression (System Organ Class – General Disorders and Administration Site Conditions).

Secondary Malignancy (such as AML, CML, and 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 of the protocol.

Reporting Serious Adverse Events within SWOG

For patients who are enrolled in a study, and have received investigational drug(s), commercial drug(s), surgery, radiation therapy, or any combination of the above, all SAEs as defined in Protocol Section 16 must be reported within 24 hours of occurrence or discovery using the on-line Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) at the CTEP-AERS Application page at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm . In rare cases where on-line CTEP-AERS reporting cannot be accessed, the site can initially report the event to the Operations Office SAE Coordinator by phone (210-614-8808), fax (210-614-0006), or email (adr@swog.org), and follow up with completion of a CTEP-AERS report as soon as access to the CTEP-AERS system has been restored.

All cases of Secondary Malignancy, including Acute Myeloid Leukemia (AML), Acute Lymphocytic Leukemia (ALL), and Myelodysplastic Syndrome (MDS) occurring in any patient who was previously or is currently on an NCI protocol must be reported via CTEP-AERS within 30 days of diagnosis. The patient's pathology report and (if available) cytogenetic report must also be submitted to the Operations Office SAE Program staff.

Investigators or their study personnel are encouraged to contact the Operations Office for guidance on whether immediate CTEP-AERS reporting is required before submitting the on-line report. Based on the grade, hospitalization, investigational status of the drug, attribution and nature (expected or unexpected) of the adverse event, the investigator will be advised whether or not to notify the Investigational Drug Branch (IDB) within 24 hours via CTEP-AERS 24hr Notification Report in addition to the complete CTEP-AERS report.

If such a report is required, once it has been submitted via CTEP-AERS as specified above, follow-up action will be as specified in Section 16 of the protocol. The specific follow-up required will depend on the factors indicated below:

1. For SAEs in patients who have received an investigational drug given under an Investigational New Drug (IND) application held by SWOG, the following must be submitted to the Operations Office within 5 calendar days:**
 - a. A copy of the first page of the printed CTEP-AERS report.
 - b. Copies of relevant clinical and/or protocol data sufficient to document the SAE and substantiate the investigator's attribution of the adverse events being reported. Supporting data which will be submitted should be indicated in the "Additional Information" section of the CTEP-AERS report. Autopsy reports should be submitted when available.
 - c. For all supporting documentation submitted for SAE reports the following is required: (1) all patient names and identifiers other than SWOG patient identification (ID) numbers must be completely obscured, (2) the SWOG protocol number and SWOG patient identification number must appear on each page submitted and be printed, typed or legibly written.
 - d. If the information does not arrive within five days, or if any of the required elements are missing, the investigator will be sent a follow-up notice with a second deadline for

submission. If there is no response to the follow-up request within one week, disciplinary action may be recommended.

This additional information is always required for SWOG-held INDs, as SWOG assumes the ultimate responsibility for the accuracy of the event code(s), grade(s), and attribution(s) in its IND report to the FDA.

2. For SAEs in patients who have received an investigational drug given under an Investigational New Drug (IND) application held by NCI, follow-up action is as follows:
 - a. Grade 5 events except those due to an unrelated event (e.g. car accident) will require supporting documentation be submitted as outlined in #1 above.
 - b. The CTEP-AERS report will be evaluated by the SAE Coordinator, and if data is needed to support, clarify, or substantiate information in the report, a request will be sent to the submitting investigator or institution by the SWOG SAE Coordinator. In the absence of such a request, supporting SAE data should not be sent automatically to the SWOG Operations Office. However, the NCI, as the IND-holder, may directly contact the investigator for substantiating information. In these instances, the NCI will request that the investigator copy SWOG on any supporting information.
 - c. If requested information is not received within five days, the investigator will be sent a follow-up notice with a second deadline for submission. If there is no response to the follow-up request within one week, disciplinary action may be recommended.
3. For SAEs in patients who have received no investigational drug given under an Investigational New Drug (IND) application (commercially approved drugs only or non-drug treatments), follow-up action is the same as for NCI-held INDs in # 2 above.

Evaluation of Serious Adverse Events

For NCI-held IND studies and commercial drug studies, evaluations of SAEs will be done by the 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 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. The exception will be any Grade 5 event that is not due to progressive disease or an unrelated event (e.g. car accident).

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

The SWOG Physician Reviewer evaluates the report, the supporting data, 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 data will be reviewed for protocol compliance by the SAE Coordinator.

Based on the SWOG Physician Reviewer's assessment he/she may recommend changes in SAE code(s), grade(s), and attribution(s). If the SWOG 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 SWOG 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 SWOG Physician Reviewer will be reflected in the entries made in the SWOG database.

If the SWOG 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 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 changes 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.

SAE's reported on SWOG-held IND studies that also meet the criteria of grade 3, unexpected, and possibly, probably, or definitely related to the investigational agent or regimen for FDA IND safety reporting will also be sent to the Study Chair for review.

For all **Grade 5** events, the coding, grading, and attribution must be reconciled between CTEP-AERS and the SWOG database.

Safety Reporting

In the case of a SWOG-held IND study, after completion of the above evaluation of a reported SAE that also meets the three criteria of unexpected; grade 3 or above; and possibly, probably, or definitely related to the investigational agent or regimen will require that a safety report be submitted to the FDA and distributed to investigators participating in trials under that IND. The drug information section and model consent form of the protocol will be amended as necessary.

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 initially reporting SAEs within twenty-four hours of discovery and submitting reports within 10 days thereafter. 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 privileges and/or conduct of a for cause Quality Assurance audit at the option of the Group Chair.

References

National Cancer Institute Cancer Therapy Evaluation Program: "NCI Guidelines For Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs," September 16, 2013

Code of Federal Regulations, Title 21, Part 312, Investigational New Drug Application

Code of Federal Regulations, Title 21, Part 56, Institutional Review Boards

Code of Federal Regulations, Title 45, Parts 160 and 164, Standards for Privacy of Individually Identifiable Health Information