

## SOUTHWEST ONCOLOGY GROUP

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**Policy Memorandum No. 23**  
**Subject:** Serious Adverse Events  
**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 NCI in *NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents*, as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (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 event occurring at any dose that results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

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 in 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 the Southwest Oncology Group should normally be reported directly to the cooperative group that coordinates the study according to the protocol guidelines, and a copy of the report provided to the SAE Program staff

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in the Operations Office. An investigator who is unclear whether or to whom to report a particular event should contact the SAE Program staff in the Operations Office at 210-614-8808 or [adr@swog.org](mailto: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). 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, *Adverse Event Reporting Requirement for NCI Investigational Agents*, including the *Adverse Event Reporting for Commercial Agents* section. 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. Newly activated studies are in CTCAE version 4.0 and many open studies are being converted to version 4.0. Version 4.0 is a major reorganization of adverse event taxonomy, done to conform to the international standard, Medical Dictionary for Regulatory Activities (MedDRA). Because of some changes and additions in this reorganization the following guidance for SWOG studies will be followed:

Deaths due to progressive disease that cannot be classified with a more specific grade 5 adverse event should be reported as Death, NOS.

“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.

“Neoplasms benign, malignant and unspecified (incl. cysts and polyps)” should not be reported as SAEs unless possibly, probably, or definitely attributable to protocol treatment. (Per NCI policy, occurrences of AML, CML and MDS in patients who are or have been on NCI protocols should be reported only on the NCI/CTEP Secondary AML/MDS Report Form.)

**Reporting Methods to be Used**

Except in special cases as specified below, the standard method of reporting SAEs on Southwest Oncology Group studies is the on-line NCI Adverse Event Expedited Reporting System (AdEERS). All adverse events which meet the reporting guidelines in Section 16 of a protocol must be entered into AdEERS and submitted on-line within 24 hours of occurrence or discovery. If this cannot be done or this deadline cannot be met, notice must be given by telephone or email to the SAE Program staff at the Operations Office within 24 hours of occurrence or discovery.

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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 on-line at the AdEERS Application page at <http://ctep.cancer.gov/reporting/adeers.html>. In rare cases where on-line AdEERS reporting cannot be done, the Operations Office SAE Program staff may give advance approval for use of AdEERS paper templates for reporting. This should not be done without first contacting the Operations Office.

When required, supporting documentation relevant to the SAE report (see the next section) must be indicated in the "Additional Information" section of the AdEERS report and submitted to the Operations Office SAE Program staff as well as to the NCI within ten calendar days.

All cases of 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 using the AML/MDS/ALL form at [http://ctep.cancer.gov/forms/33-AML\\_20Form\\_20v1.pdf](http://ctep.cancer.gov/forms/33-AML_20Form_20v1.pdf) 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 along with the form.

All supporting documentation submitted for SAE reports must: (1) completely obscure all patient names and identifiers other than the Southwest Oncology Group patient identification (ID) numbers (2) reference the Southwest Oncology Group protocol number and Southwest Oncology Group patient identification number; and (3) be printed, typed or legibly written.

**Reporting Serious Adverse Events within the Southwest Oncology Group**

Any event which meets the criteria specified in the relevant protocol is to be reported immediately (within 24 hours) to the Southwest Oncology Group Operations Office by on-line AdEERS, by phone (210-614-8808) or, during times when the Operations Office is closed, by telephone voicemail, fax (210-614-0006), or email ([adr@swog.org](mailto:adr@swog.org)).

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

If such a report is required, once it has been submitted via AdEERS 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 Southwest Oncology Group, the following must be submitted to the Operations Office within 10 calendar days:\*\*
  - a. A copy of the printed AdEERS 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 AdEERS report. All patient identifiers except Southwest Oncology Group patient ID numbers must be obscured on all forms and data submitted.
  - c. Autopsy reports should be submitted when available.

If the information does not arrive within ten 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. The AdEERS report will be evaluated by a designated Physician Reviewer, 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. In the absence of such a request, supporting SAE data should not be sent automatically to the Operations Office.
  - b. If requested information is not received within ten 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.

**\*\*\***When SWOG is not the IND-holder additional information is not always required, but will be requested when necessary to clarify the event. 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.**\*\*\***

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**

Preliminary evaluations of SAEs will be done by the Physician Reviewer as AdEERS reports are received.

For SWOG-held IND studies, additional data is always required on submitted SAEs. The Physician Reviewer's evaluation will be completed on receipt of the required data. For NCI-held IND studies and commercial drug studies, supporting data will be requested from the reporting institution only as needed, and the Physician Reviewer's evaluation will be completed once this data is received.

In all cases, the Physician Reviewer evaluates the report, the supporting data if required, 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 a nurse SAE consultant. Based on this review, the Physician Reviewer may recommend changes in SAE code(s), grade(s), and attribution(s).

If the Physician Reviewer recommends a changes in SAE **code(s)** and **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 may have made to his/her assessment of the event.

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The Physician Reviewer recommendations will also be sent to the Study Coordinator 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 a related (definitely, probably, or possibly) to an unrelated (unlikely, not) 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 will also be sent to the Study Coordinator 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 Coordinator 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.

For adverse events below grade 5, differences in SAE attributions entered into AdEERS (by the investigator) and the SWOG database (following Physician Review) will not be resolved. For all grade 5 events, the coding, grading, and attribution must be reconciled between AdEERS and the SWOG database.

**Safety Reporting**

In the case of a SWOG-held IND study, completion of the above evaluation of a reported SAE that meets the three criteria of unexpected; grade 3 or above; and possibly, probably, or definitely related to the investigational agent will trigger the following actions: The drug information section and model consent form of the protocol will be amended as necessary to reflect the SAE, and a safety report will be submitted to the FDA.

**Protocol Violation**

If a protocol violation was involved in a reported SAE, action will be at the option of the Group Chair and may include disciplinary action.

**Determination of Disciplinary Action**

Group institutions will be reviewed regularly 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 as part of their response to the audit findings.

Repeated delays in SAE reporting may result in a suspension of an institution's registration privileges. Within three to six months of reinstating the registration privileges of the institution, a repeat Quality Assurance Audit may be performed to assure compliance with SAE reporting policies.

Serious adverse events determined to be due to a protocol violation may result in a Quality Assurance Audit within two weeks. The Group Chair may, at his discretion, suspend the institution's registrations. A written explanation of actions taken and mechanisms instituted to prevent future problems will be required before registration privileges are reinstated.

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### **Serious Adverse Events on Intergroup Studies**

SAE reporting guidelines are to be followed as specified in the protocol, whether the study is coordinated by the Southwest Oncology Group or another cooperative group. SAE reports on studies coordinated by other groups should be submitted directly to the coordinating group as specified in the protocol. If AdEERS is used, Southwest Oncology Group will automatically receive the report. If another reporting mechanism is used, a copy of the report should be provided to the Southwest Oncology Group SAE Program at the Operations Office.

### **References**

National Cancer Institute Cancer Therapy Evaluation Program: "NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents," January 1, 2005

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