TOXICITY AND ADVERSE EVENT

Definition

Toxicities are any adverse event caused or possibly caused by the drugs or treatment used in the study (rather than a reaction to cancer or some other underlying disease), regardless of whether or not the event is expected.

An Adverse Event is any change in a patient’s condition from the day protocol treatment began, regardless of cause. In SWOG protocols the terms toxicity and adverse event are used interchangeably. All grades of adverse events 1 – 5 including those considered clinically insignificant must be reported on the Adverse Event Form. Document the worst Grade seen during the reporting period. Do not report an event existing prior to registration as an adverse event unless it worsens. Unless otherwise specified, all adverse events should be reported, regardless of attribution to protocol treatment.

Adverse Event reporting is a very important responsibility for the Oncology Research Professional. The patients' toxicity levels before, during, and after treatment administration are used by the SWOG Data Operations Center and study chair to determine whether the treatment dose is acceptable, and are a factor in deciding whether or not that treatment will be used in the future. This routine adverse event reporting is in addition to expedited reporting of Serious Adverse Events (see Chapter 13).

Some protocols may include instructions for the use of palliative or prophylactic agents to prevent or lessen the toxic effects of chemotherapy or other treatment. If such information is not present in the protocol, the investigator may consult with the protocol study chair.

The Cancer Therapy Evaluation Program (CTEP) provides the criteria used to grade toxicities and adverse events. SWOG protocols currently use one of two versions. The “NCI- The “Common Toxicity Criteria for Adverse Events” (CTCAE 3.0) is used on all CTEP approved protocols activated before October 2009. Version 4.0 of the “Common Toxicity Criteria for Adverse Events” (CTCAE 4.0) is used on all protocols activated after October 2009. These versions are found online at http://ctep.cancer.gov.

Adverse Event Information in SWOG Protocols

The following sections of each protocol contain important toxicity information and should be reviewed carefully.

Section 3.0 Drug Information
Lists known human toxicities for the study agents. The toxicities contained in this section of the protocol should also be listed in the informed consent form. Section 3 also contains pharmaceutical data, storage and administration instructions and supplies information.

Section 5.0 Eligibility Criteria
Outlines patient and disease characteristics required for participation in the study. Required prestudy tests noted in this section not only determine patient eligibility but also establish a baseline for future toxicity comparisons.

Section 7.0 Treatment Plan
Provides a detailed description of the entire treatment or study plan. Instructions for the use of palliative or prophylactic agents to prevent or lessen the toxic effects of chemotherapy or other treatment would also be listed here.

Section 8.0 Toxicities to be Monitored and Dosage Modifications
Details what dose changes to make if specific toxicities occur and will describe ancillary treatment allowed to manage or prevent a toxicity, or ancillary drugs not allowed during protocol participation. This section also specifies which toxicity criteria version should be used and provides contact information for treatment and dose modification questions.

Section 9.0 Study Calendar
Indicates when toxicity assessments are required, the protocol treatment schedule, and specific labs to be done. The footnotes contain valuable information on toxicity assessments beyond the days specified on the calendar. This section also lists additional prestudy tests that are not required for eligibility but should be done in accordance with good medical practice to ensure patient safety. As noted in section 5.0, these tests also help establish a baseline for future toxicity comparisons. Minor deviations are allowed if they do not jeopardize patient safety. If there are significant deviations in the values of these tests, the Study Chair must be contacted prior to patient registration. If an individual test is deemed unnecessary by the treating PI, the rationale for not conducting the test must be documented in the medical record.

Section 14.0 Data Submission Schedule
Provides the required schedule for routine adverse event reporting via submission of case report forms. This schedule generally matches the toxicity assessment schedule listed in Section 9.0.

Section 16.0 Ethical and Regulatory Considerations
Instructions for reporting Serious Adverse Events (SAEs). (See SAE - Chapter 13.)

Online Data Submission of Adverse Events

On August 15th, 2006 it became mandatory for ORPs to report adverse events using online data submission. For studies activated before April 2012, online data submission is accessed via the “Pre-Rave Data Submission” link on the CRA Workbench. Protocols activated after April 2012 use the Medidata Rave® system for all data collection including Adverse Events.

If at any time you have questions, please feel free to call the SWOG Data Operations Center at (206) 652-2267.
Reporting Adverse Events

Adverse Event Grading

Always use the NCI – Adverse Event/Toxicity criteria specified in the protocol (either, v 3.0 or v 4.0). Each adverse event/toxicity in the NCI Criteria is defined in terms of severity, or grades. Adverse events/toxicities are graded using a numerical scale from 1 - 5; the grade number gets higher as the severity of the adverse event/toxicity increases.

1 = Mild
2 = Moderate
3 = Severe or medically significant but not immediately life-threatening
4 = Life threatening consequences
5 = Death related to AE

Not all grades are defined for every adverse event. There are many adverse events that have limited grading and Version 3 requires you to also consider coding related toxicities. Almost half of the adverse events in the NCI – Common Toxicity Criteria (CTCAE 3.0 or v 4.0) are graded with less than the full 1-5 scale (limited grading). The table on the following page lists some examples of adverse events with limited grade and “also consider” definitions.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE-v4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>mild hair loss</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>pronounced or total hair loss</td>
</tr>
<tr>
<td></td>
<td>3-5</td>
<td>not defined</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>1</td>
<td>not defined</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>not defined</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life threatening</td>
</tr>
<tr>
<td>CTCAE-v3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
<td>1 = 5 - &lt;10%</td>
</tr>
<tr>
<td>Also consider: vomiting, dehydration, diarrhea</td>
<td>2</td>
<td>2 = 10 - &lt;20%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3 = ≥20%</td>
</tr>
</tbody>
</table>

The online Adverse Event forms on the CRA Workbench and in Medidata Rave® are programmed to use only the appropriate grades for each event according to the CTCAE-3 or CTCAE-4. If you try to select a grade that is not defined in the CTCAE, you will get a data entry error. When documenting events in the Rave system, please use the drop down boxes to select grade and attribution codes.
Attribution Coding

The protocol may also require you to report an “attribution code” to indicate, in the opinion of the investigator how likely, the condition observed is due to protocol treatment. Attribution codes range from 1 to 5.

1. Unrelated
2. Unlikely
3. Possible
4. Probable
5. Definite

Status Codes

SWOG studies requiring complete reporting will also collect status in addition to grade and attribution. Complete reporting studies are generally SWOG phase II trials exploring investigational new drugs. The status code describes the state of the adverse event at various points throughout the study.

Status codes range from 1 to 3.

1. New
2. Continues at same or lower grade
3. Increased grade OR improved then worsened

Cycle Specific Reporting

For studies that use cycle specific adverse event reporting, adverse events for each cycle should be reported from the time of the first treatment of the specific cycle until the beginning of the following cycle. The “Date of the most recent adverse event assessment” should be a date equal to or more recent than the Date of last treatment”. All adverse events occurring prior to initiation of the next cycle must be reported. An adverse event term should be reported only once per cycle and the worst grade observed during that cycle should be documented.

Other Adverse Event Reporting Periods

Protocols that involve daily treatment over a long period will have reporting periods defined for adverse events. This may be monthly or every 3 months, for example. Remember to document the worst grade observed during each reporting interval as defined on the form or in the protocol. Adverse events that persist continuously from one period to the next should only be reported once, unless the grade becomes more severe at a later assessment or unless the adverse event resolves and then reoccurs during a subsequent period.

Recent Developments

Studies activating in 2017 and later that involve investigational new drugs (IND), you will be seeing an integrated adverse events/SAE reporting form in Rave. The form looks like this:
This may look intimidating, but for most events you will only need to complete the adverse event term, grade, attribution and check off a few other fields. If the event you enter is determined to be a potentially serious adverse event for the study, more forms will appear. These forms are intended to replace the requirement for separate SAE reporting. All of your routine and serious adverse events will be documented in Rave.

These forms will capture the date of the patient’s initial treatment cycle and that date will display on all subsequent forms. Each cycle you will need to enter the start date for the specific treatment cycle that you are reporting, the cycle one form will be the only time the dates at the top of the form will be the same.

**Cycle 1 form**

<table>
<thead>
<tr>
<th>* Start date of this course/cycle</th>
<th>10 Aug 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date of first course/cycle (derived)</td>
<td>10 Aug 2017</td>
</tr>
</tbody>
</table>

**Cycle 2 form**

<table>
<thead>
<tr>
<th>* Start date of this course/cycle</th>
<th>30 Aug 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date of first course/cycle (derived)</td>
<td>10 Aug 2017</td>
</tr>
</tbody>
</table>

For questions about reporting routine adverse events, contact your study data coordinator at the SDMC in Seattle. For questions about serious adverse events, contact the SAE coordinator at the Operations Office in San Antonio, adr@swog.org