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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. Unless otherwise specified, document the worst Grade seen during the reporting period. Some studies with more detailed adverse event reporting requirements ask that each grade be reported as a separate event; this will be stated in the form instructions when necessary. Do not report an event existing prior to registration as an adverse event unless it worsens in Grade or reoccurs after previously resolving. Furthermore, when labs are drawn on day 1 of a cycle and prior to the initiation of study drug, any adverse events that result should be reported on the AE Form for the prior cycle since they pertain to treatment from the previous cycle. 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. Each trial has an objective to evaluate toxicities so that study leadership evaluates the safety of experimental regimens as well as its effectiveness. 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 adverse events, called the “Common Terminology Criteria for Adverse Events” or CTCAE for short. The majority of SWOG protocols currently use one of two versions. Version 4.0 of the CTCAE was used for all protocols activated after October 2009 until version 5.0 of the CTCAE was published in November 2017. All SAE reporting was transitioned to CTCAE v5.0 in April 2018. All versions of the CTCAE can be 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 5.0 Eligibility Criteria
Outlines patient and disease characteristics required for participation in the study. Required pre-study 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 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 may also list additional pre-study tests that are not required for eligibility but should be done in accordance with good medical practice to ensure patient safety and establish a baseline for future toxicity comparisons.

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) and Adverse Events of Special Interest (AESIs). (See SAE - Chapter 13.) These instructions may be included in Section 8.0 in some protocols.

Online Data Submission of Adverse Events
All adverse event reporting is done through 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. Please note that newer protocols also use Medidata Rave® to initiate SAE reporting through a CTEP-AERS integration tool (see end of this Chapter for more information).

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 Grades

Always use the NCI CTCAE version specified in the protocol. Each adverse event in the NCI CTCAE is defined in terms of severity, or grades. Adverse events are graded using a numerical scale from 1 - 5; the grade number gets higher as the severity of the adverse event increases. The CTCAE provides specific clinical descriptions of each grade for each adverse event based on this general guideline:

1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4 = Life-threatening consequences; urgent intervention indicated.
5 = Death related to AE.

Not all grades are defined for every adverse event. Almost half of the adverse events in the CTCAE are graded with less than the full 1-5 scale (limited grading). The following table lists some examples of adverse events with limited grade.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>Hair loss of &lt;50% of normal for that individual…</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hair loss of &gt;=50% normal for that individual…</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>ANC &lt;1000/mm3 with a single temperature of &gt;38.3 degrees C (101 degrees F) or a sustained temperature of &gt;=38 degrees C (100.4 degrees F) for more than one hour</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life-threatening consequences</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 relevant CTCAE for the study. 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, always use the drop down boxes to select term, grade and attribution codes.
Attribution Codes
The protocol will likely 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. Attribution coding must be done by the investigator, not the patient or ORP.

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

Status Codes
Some SWOG studies will also collect status in addition to grade and attribution. 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. Unless otherwise specified, 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. Unless otherwise specified, document the worst grade observed during each reporting interval as defined on the form or in the protocol.

CTEP-AERS Integration
The NCI has created Rave Adverse Events forms that integrate directly with the CTEP-AERS expedited reporting system for SAEs, in order to reduce duplication of data entry. As of May 2019, ten active studies use this form to collect adverse events, and all new SWOG studies developed in the future will use the integrated form. For studies using this form, SAEs must be entered in Rave at the time the site is made aware of them, even if this is not at the end of a cycle or reporting period.
The Adverse Events: Report form with CTEP-AERS integration looks like this:

This may look intimidating, but for most events you will only need to complete the standard adverse event term, grade and attribution fields, then check off any of the listed outcomes the adverse event resulted in.

These forms will capture the date of the patient’s initial treatment cycle and that date will display on all subsequent forms. On each cycle, you will also need to enter the start date for the specific treatment cycle. The Cycle 1 Adverse Event form will be the only time the dates at the top of the form will be the same.

Cycle 1 form:

- Start date of this course/cycle: 10 Aug 2017
- Start date of first course/cycle: 10 Aug 2017

Cycle 2 form:

- Start date of this course/cycle: 30 Aug 2017
- Start date of first course/cycle: 10 Aug 2017

Once all AEs have been entered, you will navigate to the “Expedited Reporting Evaluation” form in the same cycle in Rave and submit this form. The system will then assess whether expedited reporting is recommended and provide you a link directly to a CTEP-AERS with the preliminary information already filled out:
For questions about reporting routine adverse events, contact your study data coordinator at the SWOG Data Operations Center in Seattle. For questions about Serious Adverse Events, contact the SAE Program at the SWOG Operations Office in San Antonio at adr@swog.org.