TOXICITY AND ADVERSE EVENT

Definition

An Adverse Event (AE) is any unfavorable and unintended change in a patient's condition from the day protocol treatment began, regardless of cause. A toxicity is 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). You may see both terms used in SWOG protocols depending on the context; however, patient assessments and reporting should encompass the broader category of adverse events.

Unless otherwise specified, all grades of adverse events (1-5), including abnormal laboratory findings, must be reported on the study's Adverse Events Form (AE Form) regardless of attribution to protocol treatment or clinical significance. If the AE Form does not collect start and end dates for each adverse event, report the worst Grade seen during the reporting period. If the AE Form does collect start and end dates, report each grade of an adverse event as a separate entry. Do not report a symptom or condition existing prior to initiation of study treatment as an adverse event unless it worsens in grade or reoccurs after previously resolving.

Adverse event reporting is a very important responsibility for the Oncology Research Professional. Evaluating the frequency and severity of toxicities is almost always a clinical trial objective, to ensure that experimental regimens are evaluated for safety as well as 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 Serious Adverse Event (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 and adverse event 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 Dose Modifications
Details what dose changes to make if specific toxicities occur and may describe ancillary treatment suggested to manage or prevent toxicities. This section also specifies which CTCAE version should be used for AE reporting and provides contact information for treatment, toxicity and dose modification questions. In newer protocols, also notes whether the protocol utilizes the Rave®/CTEP-AERS integration and includes instructions for reporting Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs).

Section 9.0 Study Calendar
Indicates when adverse event assessments are required, the protocol treatment schedule, and specific labs to be done. The footnotes contain valuable information on adverse event 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 adverse event 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 newer 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 about online data submission, 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 term in the CTCAE is defined in terms of severity, or grade. 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 term 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 term. Almost half of the adverse event terms in the CTCAE are graded with less than the full 1-5 scale (**limited grading**). The following table lists some examples of adverse event terms with limited grading.

Adverse Event	Grade	Definition
CTCAE v5.0		
Alopecia	1	Hair loss of <50% of normal for that individual…
	2	Hair loss of >=50% normal for that individual…
	3 - 5	not defined
Febrile Neutropenia	1	not defined
	2	not defined
	3	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour
	4	Life-threatening consequences

The online Adverse Event Forms on the CRA Workbench and in Medidata Rave® are programmed to allow 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 reporting AEs in the Rave® system, always use the drop-down menus 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 it is that 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

Start and End Dates

SWOG studies with registration intent will also collect start and end dates for adverse events. For guidance on recording adverse event start and end dates, please refer to the protocol-specific Form Instructions and the 'CTEP Guidance for Recording Adverse Event Start and End Date in Rave', available here.

Cycle-Specific Reporting

Most SWOG studies require cycle-specific adverse event reporting. On a given cycle, adverse events identified from the time of the first treatment on that cycle until the beginning of the following cycle must be reported. The "Date of the most recent adverse event assessment" should be a date equal to or more recent than the "Date of last treatment" on that cycle. All adverse events occurring prior to initiation of the next cycle must be reported. Furthermore, when labs are drawn on Day 1 of a cycle and prior to the patient receiving study drug on that cycle, any abnormal laboratory findings should be reported on the AE Form for the prior cycle since they pertain to treatment from the previous cycle. If the AE Form does not collect start and end dates for each adverse event, an adverse event term should be reported only once per cycle and the worst grade observed during that cycle should be reported.

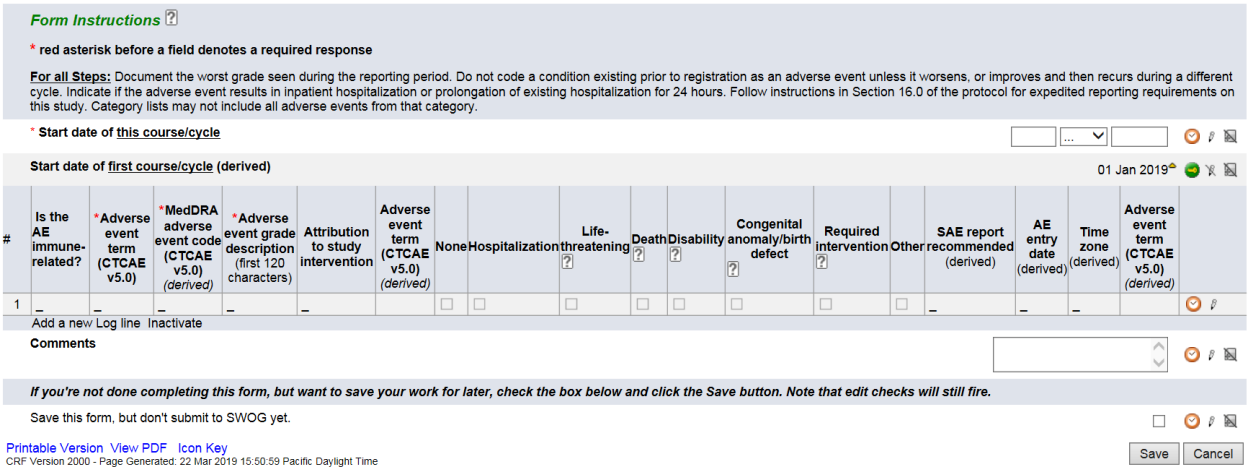
Other Adverse Event Reporting Periods

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, report the worst grade observed during each reporting interval as defined on the form or in the protocol.

CTEP-AERS Integration

The NCI has created Adverse Events forms in Rave® that integrate directly with the CTEP-AERS expedited reporting system for SAEs, in order to reduce duplication of data entry. Section 8 of the protocol will indicate whether the study uses the Rave®/CTEP-AERS integration. For studies using the integration, SAEs must be entered in Rave® at the time the site learns of the event, 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:



Form Instructions

* red asterisk before a field denotes a required response

For all Steps: Document the worst grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens, or improves and then recurs during a different cycle. Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for 24 hours. Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study. Category lists may not include all adverse events from that category.

* Start date of this course/cycle

Start date of first course/cycle (derived) 01 Jan 2019

#	Is the AE immune-related?	*Adverse event term (CTCAE v5.0)	*MedDRA adverse event code (CTCAE v5.0) (derived)	*Adverse event grade description (first 120 characters)	Attribution to study intervention	Adverse event term (CTCAE v5.0) (derived)	None	Hospitalization	Life-threatening	Death	Disability	Congenital anomaly/birth defect	Required intervention	Other	SAE report recommended (derived)	AE entry date (derived)	Time zone (derived)	Adverse event term (CTCAE v5.0) (derived)
1	_	_	_	_	_										_	_	_	

Add a new Log line Inactivate

Comments

If you're not done completing this form, but want to save your work for later, check the box below and click the Save button. Note that edit checks will still fire.

Save this form, but don't submit to SWOG yet.

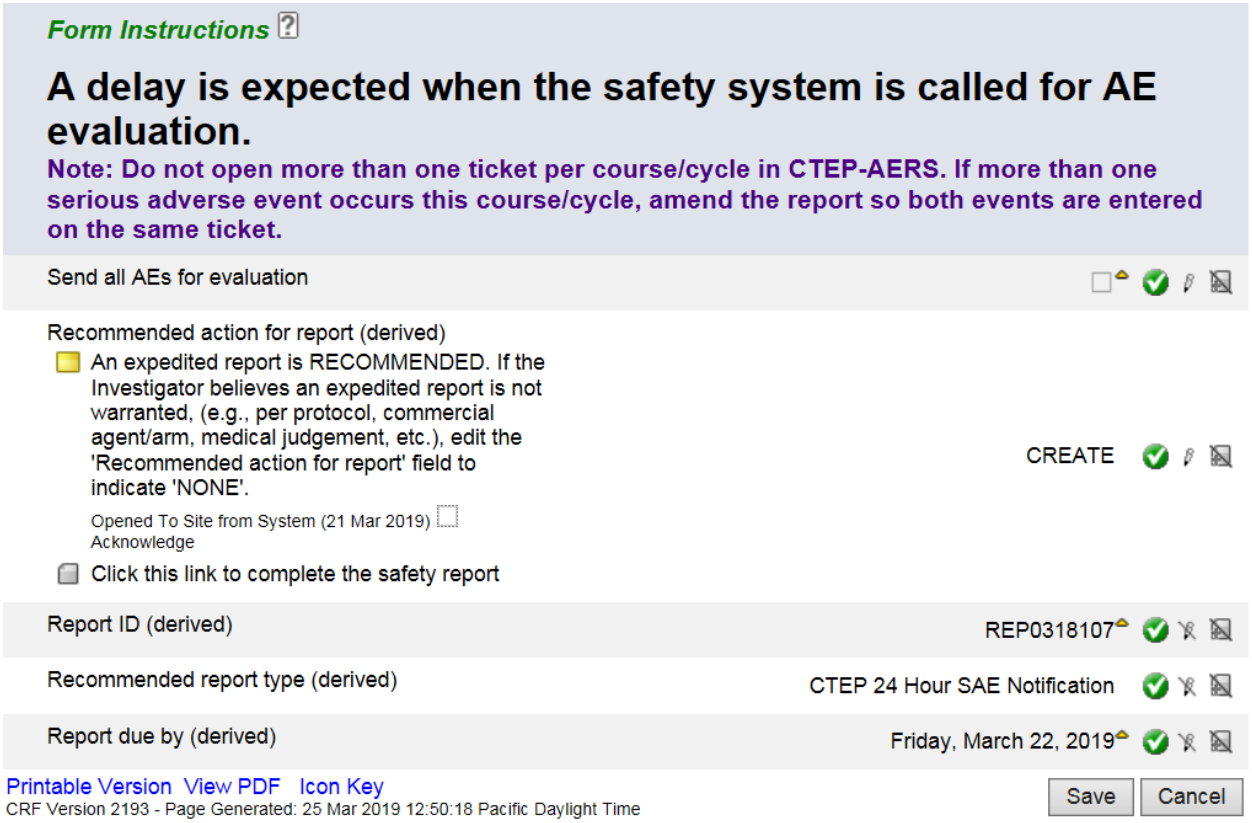
Printable Version View PDF Icon Key
CRF Version 2000 - Page Generated: 22 Mar 2019 15:50:59 Pacific Daylight Time

Save Cancel

This may look intimidating, but for most studies 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. If an event is not considered serious based on the reporting criteria listed in the protocol, then the appropriate outcome to check is “None.”

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.

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 (see screenshot below). The system will then assess whether it believes expedited reporting is recommended and provide a direct link to a CTEP-AERS report with the preliminary information pre-filled based on what was entered in Rave®. The recommended action does not necessarily need to be taken; the Investigator should use their judgment, referring to the protocol requirements for expedited reporting in protocol Section 8 or Section 16.



If the AE Form for any given cycle is amended, it must be re-submitted for evaluation by navigating once more to the Expedited Reporting Evaluation Form, checking the box to “Send all AEs for evaluation” and saving the form. This action must be completed, even if you know that an expedited report will not be required. Every time an AE Form is amended, an automatic query will post on the Expedited Reporting Evaluation Form to remind you to take this action.

AE Forms that both utilize the Rave®/CTEP-AERS integration and collect AE start and end dates include more complicated programming to link ongoing adverse events across cycles and reduce the need to duplicate data entry across cycles. If you are not familiar with the functionality of these forms, we recommend reaching out to your study data coordinator with any questions.

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 Network Operations Center in San Antonio at adr@swog.org.