Serious Adverse Event Reporting

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Contact SWOG SAE Team

- Contact SWOG first with all SAE questions, including technical support issues.
  - SAE Email: adr@swog.org
  - SAE Phone: 210-614-8808, Option 3, then Option 7

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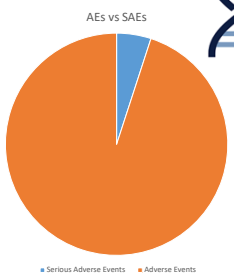
Serious Adverse Events

- SAEs are a subset of all adverse events collected.
- The reporting of SAEs is in addition to, and does not replace, the necessity of adequately reporting adverse events on the case report forms and in the final results of the clinical trial.



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CTCAE

- CTCAE = Common Terminology Criteria for Adverse Events
  - Current version is 5.0.
- The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology used for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.
  - Grade refers to the severity of the AE.
- The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE.

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CTCAE Adverse Event Grades

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

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Attribution

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to Investigational Agent / Intervention	Unrelated	The AE is clearly NOT Related to the intervention
	Unlikely	The AE is Doubtfully Related to the intervention
Related to Investigation Agent / Intervention	Possible	The AE May be Related to the intervention
	Probable	The AE is Likely Related to the intervention
	Definite	The AE is Clearly Related to the intervention

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SAE Reporting Criteria Found In:

Section 8 **OR** Section 16

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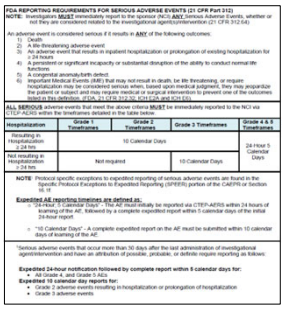
SAE Reporting Table

Example of SAE Reporting Criteria for Investigational Agent



FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agents/intervention (21 CFR 312.64).

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization/ ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization/ ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-hour report" - A complete report can initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

*Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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SAE Reporting Table

Example of SAE Reporting Criteria for Commercially Available Agent

Grade 4, Unexpected, *and* Possibly, Probably, Definitely Related

OR

Grade 5

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b]

[a] **This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.**

[b] **Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.**

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Additional Reporting Requirements

A subsection that may contain information on events that are exceptions to expedited reporting as well as events that require expedited reporting regardless (AESI)

16.1 Adverse Event Reporting Requirements

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a CTEP-IND:**

1) **Group-specific instructions.**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below also require expedited monitoring for this trial:

- *Thromboembolic events, any Grade regardless of attribution*

3) For study arm(s)[applicable study arm(s)], the adverse events listed below do **not** require expedited reporting via CTEP-AERS:

- *≤ Grade 4 myelosuppression*
- *≤ Grade 4 infection*

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SPEER

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- SPEER = Specific Protocol Exceptions to Expedited Reporting
- This subset of AEs (SPEER) is a list of events that are protocol-specific **exceptions to expedited (SAE) reporting** to NCI.
- Report AEs on the SPEER as SAEs only if they *exceed* the grade noted in parentheses next to the AE in the SPEER.
- If the protocol uses multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [nr 2060]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Eye disorders - Other (optic neuritis retrobulbar)[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[1]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		

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SPEER

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Reminder that the SPEER column only applies to SAE reporting.

It does not apply to routine AE reporting.

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		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		

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Reporting a Death

Any death while on treatment or within 30 days of the last dose of study agent must be reported via expedited reporting (CTEP-AERS).

CTCAE Terms:

- Death Attributable to CTCAE Term
- Death, NOS (Only used if the death cannot be attributed to an existing Grade 5 CTCAE term.)
- Sudden Death NOS
- Disease Progression

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Pregnancy Reporting

Refer to SAE Reporting Section of the Protocol

- Report via CTEP-AERS
- NCI Pregnancy Reporting Form must also be completed.
  - NCI Pregnancy Reporting Form

CTCAE Terms:

- Pregnancy (Study Participant)
- Pregnancy Loss
- Death Neonatal

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Secondary Malignancies

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under an IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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Second Malignancies

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

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How to Report an SAE

SAE Reporting is done electronically through CTEP-AERS.

- For older protocols, SAE reporting should be done directly in CTEP-AERS.
- For newer protocols using the Rave/CTEP-AERS integration, the report will be generated through Rave, then completed in CTEP-AERS.

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Rave/CTEP-AERS Integration

- Information on the Rave/CTEP-AERS integration
  - Please contact adr@swog.org with any integration questions/issues
- When utilizing the Rave/CTEP-AERS integration, keep in mind that the system is only loaded with basic rules for reporting.

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Rave/CTEP-AERS Integration

- There will be times when the system recommends reporting an event via CTEP-AERS but per protocol, an event does not meet criteria for expedited reporting.
- SAEs should always be reported based on the protocol.
- The Rave/CTEP-AERS integration recommendation is just that - a recommendation; it is not a mandate to report.
- The opposite can also be true. The system may not recommend the reporting of an event via expedited report, but per protocol, the event meets criteria for expedited reporting. The event may also be an adverse event of special interest (AESI) that requires reporting per special instructions in the protocol.

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Rave/CTEP-AERS Integration

- Expedited (SAE) reporting should be done based on protocol-specified criteria. If the automated recommendation in Rave does not match the protocol, follow the protocol.
  - Sites can email adr@swog.org or call 210-614-8808 anytime with SAE questions.
- If sites are amending a CTEP-AERS report and find an item/section that is unable to be changed (greyed out), this indicates the information is derived from Rave. The data must be changed directly in Rave.
- The Expedited Reporting Evaluation form must always be run. Anytime the data in a cycle is changed, this evaluation should be re-run to ensure no changes are needed to an existing CTEP-AERS report.

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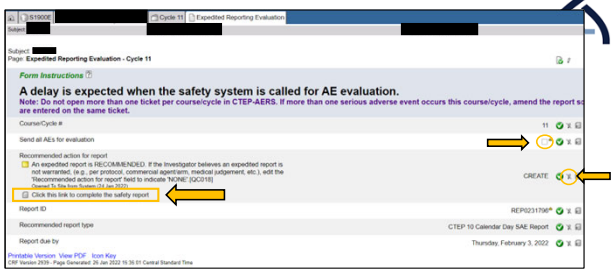

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Adverse Events: Report

#	Adverse Event (Verbatim term)	*Adverse event term (CTCAE v5.0)	*What is the description of the toxicity? (first 120 characters)	Start Date	End Date	Ongoing	Relationship to Study Treatment	Hospitalization (initial or prolonged)	Life Threatening	Death	Disability or Permanent Damage	Congenital Anomaly or Birth Defect	Other Serious (Important Medical Events)	What action was taken with study treatment?	*AE Number	SAE report recommended	*Date/Time of Collection
1	Back Pain	Back pain	(1) Mild pain	20 Oct 2021		Yes	Unrelated	No	No	No	No	No	No	Dose Not Changed	AE99-8D42262B58D84E7DB89AF2E673BDF834	No	26 Oct 2021 01 44 31 PM
2	dyspnea	Dyspnea	(3) Shortness of breath at rest; limiting self care ADL	20 Jan 2022		Yes	Unrelated	Yes	No	No	No	No	No	Drug Interrupted	AE11-D8EDA7F92CFC4E582D38F86976B56653	Yes	24 Jan 2022 02 16 36 PM

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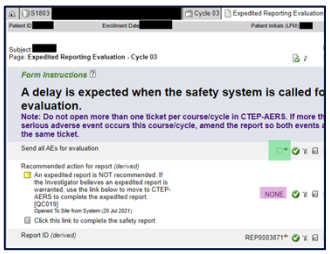
Expedited Reporting Evaluation Form

- The Expedited Reporting Evaluation form must be run each time changes are made to the AE Report form.
- To run the evaluation, select the checkbox (highlighted here in green), then save the form.
  - If the checkbox does not display, click the pencil icon to run the evaluation.
- A recommended action will display (highlighted here in pink). This is only a recommendation, follow reporting guidelines in the protocol or consult adr@swog.org.



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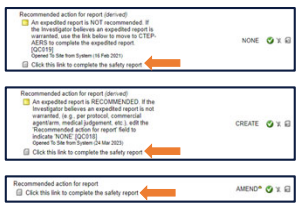
Expedited Reporting Evaluation Form

NONE = no SAE report is being recommended by the automated rules engine, but always refer to the protocol

CREATE = an SAE report is being recommended by the automated rules engine, but always refer to the protocol

AMEND = an amended SAE report is being recommended because new/updated data has been reported on the AE Report form



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Expedited Reporting Evaluation Form Tips

- Each time the AE Report form is updated, the Expedited Reporting Evaluation form must be manually run by sending all AEs for evaluation.
- Pop-up blockers must be disabled for the link on the Expedited Reporting Evaluation form to work.
- The CREATE, AMEND, and NONE recommendations are dynamic – they will change based on the current submitted data.
  - Example: Once a CTEP-AERS report is submitted for Cycle X, the recommendation in Rave will change from CREATE to NONE since no further action is needed at that time. When data on the same cycle's AE Report form changes, the recommendation in Rave will change from NONE to AMEND, indicating that an amended CTEP-AERS report should be submitted.
- A link to create or amend a report in CTEP-AERS is found on the Expedited Reporting Evaluation form, regardless of the recommendation. This allows sites to override the recommendations at any time.

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SAEs and Audits

- SAEs Reported Late
  - If no date of discovery is provided, SWOG uses the date the report was submitted to SWOG minus the date of event to determine late reporting.
  - If the date of discovery is different from the date of the event, please enter it in CTEP-AERS Section 3: Describe Event.
- SAEs Reportable to Local Institutional Review Board (IRB)
  - Varies due to local IRB guidelines. Check with your IRB.
- SAEs Reportable to NCI Central Institutional Review Board (CIRB)
  - Use the CIRB algorithm to determine reporting.

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Serious Adverse Events - FAQs

What does "Expedited Reporting" mean?

- Expedited reporting is the term for reporting an adverse event (AE) that has become a Serious Adverse Event (SAE). The terms SAE Reporting and Expedited Reporting may be used interchangeably.

Source: National Cancer Institute. (2013). Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs [PDF], Section 2.1.8.

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Serious Adverse Events - FAQs

I'm not sure if this AE requires SAE reporting, should I submit a report just in case?

- If unsure, the SWOG SAE Team would prefer that you contact us by email at adr@swog.org or phone at 210-614-8808 (Option 3, then Option 7) to confirm the need to report before spending time submitting an unnecessary report.

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Serious Adverse Events - FAQs

What is the deadline for submitting an SAE report to SWOG?

- Reporting timeframes are found in the SAE reporting tables within the protocol. SAE tables are found in Section 8 or Section 16 of the protocol.
- It is important to note that the 'submission due dates' in Rave or in the automated CTEP-AERS emails are not true deadlines; these dates only reflect the date after which CTEP-AERS will automatically delete unsubmitted reports.
- SWOG makes every effort to notify sites if they have a pending report that will soon be deleted, but sites are responsible for reporting within protocol-specified timeframes.

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Serious Adverse Events - FAQs

Rave is recommending an SAE report, but the recommendation does not match the SAE reporting requirements in the protocol. Should an SAE report be submitted based on the recommendations in Rave?

- The Rave recommendations are based on very basic rules and are often incorrect. SAEs should be submitted per protocol guidelines. adr@swog.org can be contacted anytime for guidance.

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Serious Adverse Events - FAQs

When a patient is on a treatment arm with both investigational and commercial agents, should both the investigational and commercial SAE reporting tables be used to determine reporting timeframes?

- No - when a commercial agent is used on the same treatment arm as an investigational agent, the entire combination is then considered an investigational intervention. In this situation, only the investigational SAE reporting table should be used to determine expedited reporting.

Source: National Cancer Institute. (2013). Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs [PDF], Section 5.4.

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Serious Adverse Events - FAQs

Adverse Events were submitted in Rave. Then, the Expedited Reporting Evaluation was submitted. I thought that one of the AEs should be reported as an SAE per protocol, but the CTEP-AERS rules engine did not recommend this reporting. Is any further action required?

- The CTEP-AERS system is pre-loaded with basic rules for reporting.
  - These rules are used to help determine whether AEs require expedited reporting.
  - It is possible that an AE won't trigger the automated rules but still requires reporting as an SAE.
  - It is also possible that the rules may recommend an SAE report, but one is not required.
- If the event doesn't meet protocol-specified reporting rules, it does not require expedited reporting.
- Best practice is to use the system recommendations as a reminder to check the protocol to ensure that the event does not require reporting; the automated RAVE recommendations for SAE reporting are not always correct.
- If in doubt as to whether an SAE report is required per protocol-specified criteria, contact the SWOG SAE Coordinators for assistance at adr@swog.org.

Source: CTEP-AERS Help Resources - Reporting AEs for Rave Users

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CTEP-AERS Home Page

Link to CTEP-AERS Home Page

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SAE Resources

- SWOG SAE TEAM
  - Contact first with all SAE questions, including technical support issues.
    - SAE Email: adr@swog.org
    - SAE Phone: 210-614-8808, Option 3, then Option 7
- NCI Guidelines for Investigators: Adverse Event Reporting Requirements
- Information on the CTEP-AERS application
- Information on the Rave/CTEP-AERS integration
  - Please contact adr@swog.org with any integration questions/issues

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