Serious Adverse Events

Reporting and Updates

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SAE Reporting Criteria Found In:

- 8/22/2024 CTEP Memo (overrides protocol for investigational treatment arms)
- Section 8 of SWOG Protocols
- Section 16 of SWOG Protocols (older protocols only)

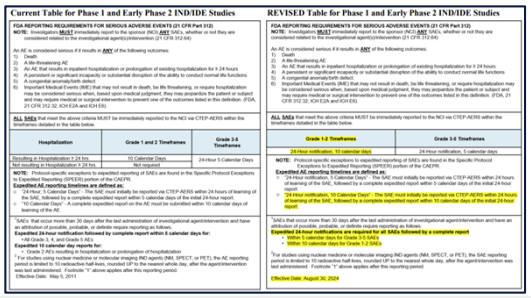
SWOG SAE Team

Contact first with all SWOG SAE questions, including technical support issues.

SAE Email: adr@swog.org

SAE Phone: 210-614-8808, Option 6

Phase I and Early Phase II Trials

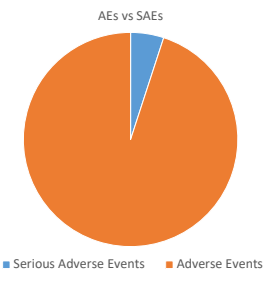


Current Table for Phase 1 and Early Phase 2 IND/IDE Studies

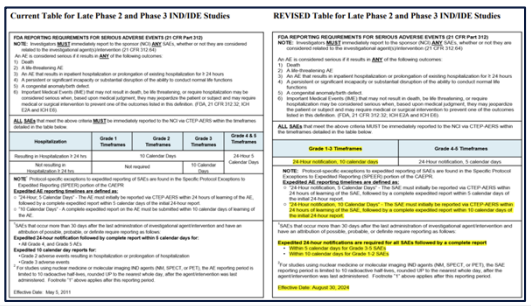
REVISED Table for Phase 1 and Early Phase 2 IND/IDE Studies

Serious Adverse Events

- SAEs are a subset of all adverse events collected.
- The reporting of SAEs is in addition to, and does not replace, reporting routine adverse events.



Late Phase II and Phase III Trials



Current Table for Late Phase 2 and Phase 3 IND/IDE Studies

REVISED Table for Late Phase 2 and Phase 3 IND/IDE Studies

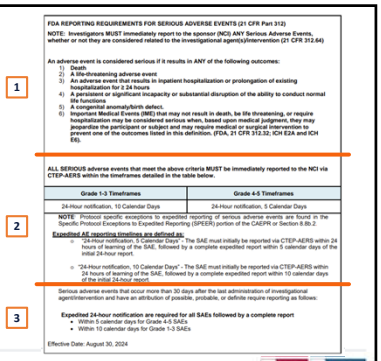
SAE Reporting Table

Example of SAE Reporting Criteria for Investigational Agents

Step 1: Is the AE serious?

Step 2: If serious, how quickly does it need to be reported?

Step 3: If it's been > 30 days since the patient last received investigational study drug, refer to the bottom of the SAE Table.



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 agent(s)/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 (IME) 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 participant 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).

1

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.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 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 8.8b.2.

2

Expedited AE reporting timelines are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

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:

3

Expedited 24-hour notification are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

Effective Date: August 30, 2024

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.

SAE Reporting Table

Example of SAE Reporting Criteria for Commercially Available Agent

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

OR

Grade 5

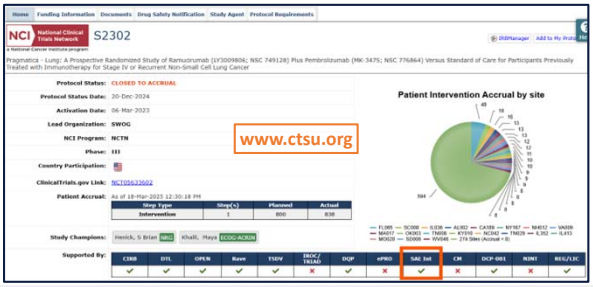
ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS

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

[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.

How to Know if a Trial Uses Rave/CTEP-AERS Integration



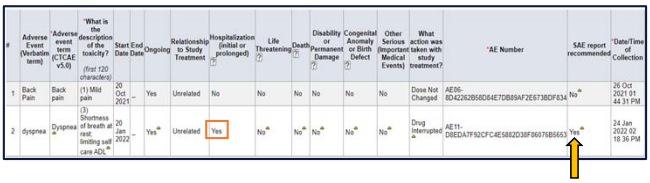
Expectedness

- **Expectedness for Investigational Drugs**
  - Expected = listed as a known risk in the Investigator's Brochure
  - Unexpected = not listed in the Investigator's Brochure
- **Expectedness for Commercial Drugs**
  - Expected = listed as a known toxicity in the Package Insert
  - Unexpected = not listed in the Package Insert

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.
- The Rave/CTEP-AERS integration recommendation is just that - a recommendation; it is not a mandate to report.

Rave Form
Adverse Events: Report



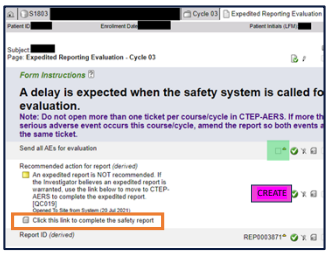
#	Adverse Event (Verbatim term)	*Adverse event term (CTCAE v5.0)	*What is the description of the toxicity? (first 120 characters)	Start Date	End Date	Ongoing	Relationship to Study Treatment	Hospitalization (initial or prolonged)	Life Threatening	Death	Disability or Permanent Damage	Congenital Anomaly 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	AE96-8D42262B58D84E7DB85AF2E673BDF834	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-D8EDA7F92CFC4E582D38F86976B5663	Yes	24 Jan 2022 02 18 36 PM

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.
- 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.

Rave Form
Expedited Reporting Evaluation

- 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 8/22/2024 CTEP Memo or consult adr@swog.org.



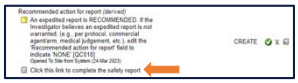
What is the deadline for submitting an SAE report to SWOG?

- Reporting timeframes are found in the SAE reporting tables. SAE tables are found in the 8/22/2024 CTEP Memo, 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 timeframes specified in the protocol or the 8/22/2024 CTEP Memo.

Rave Form
Expedited Reporting Evaluation

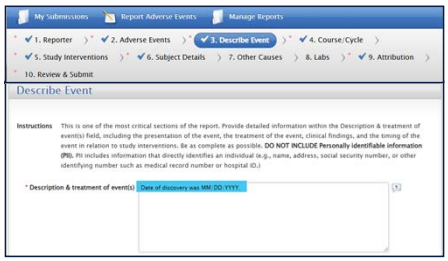
NONE = no SAE report is being recommended by the automated rules engine

CREATE = an SAE report is being recommended by the automated rules engine



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

When reporting SAEs in CTEP-AERS, please add the date of discovery into *CTEP-AERS Section 3: Describe Event*.



Without this date, SWOG may assume the SAE was reported late, and this can lead to major deficiencies during audits.

SPEER

- 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 1) they *exceed* the grade noted in parentheses next to the AE in the SPEER *and* 2) the AE is serious.
- 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) [n= 2069]			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]		

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

SPEER

Reminder that the SPEER column only applies to SAE reporting.

It does not apply to routine AE reporting.

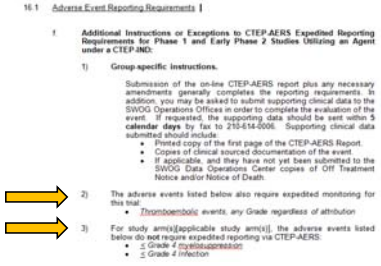
Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Eye disorders - Other (optic neuritis, retrobulbar)[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	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]		

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 adverse event reporting unless otherwise specified in the protocol.

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

Pregnancy Reporting

Refer to SAE Reporting Section of the Protocol

- Report via CTEP-AERS
- CTEP Pregnancy Reporting Form must also be completed and uploaded to SDP.
  - CTEP Pregnancy Reporting Form

CTCAE Terms:

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

Reporting a Death

Any death while on treatment or within 30 days of the last dose of study agent must be reported as a serious adverse event.

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

SAE Resources

- SWOG SAE Resource Page – additional resources here
- SWOG Expedited Reporting Submission Guide – complete guide
- SWOG SAE Reporting Flowchart
- 8/22/2024 CTEP Memo re: Global Safety Update
- List of Trials Using Updated SAE Tables
- NCI Guidelines for Investigators: Adverse Event Reporting Requirements
- Information on the CTEP-AERS application
- Information on the Rave/CTEP-AERS integration
- SWOG SAE Escape Room

Serious Adverse Events - FAQ

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 to confirm the need to report before spending time submitting an unnecessary report.

Questions?

Email adr@swog.org

Serious Adverse Events - FAQ

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.

BREAK

10:25 AM – 10:40 AM