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 6

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

SAE Reporting Criteria Found In:

Section 8 **OR** Section 16

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.

1

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 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).

2

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; 5 Calendar Days" - The AE must 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.

3

[1]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

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.**

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*

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)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea Dry mouth		***Diarrhea (Gr 3)*** ***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		

SPEER

Reminder that the SPEER column only applies to SAE reporting.

It does not apply to routine AE reporting.

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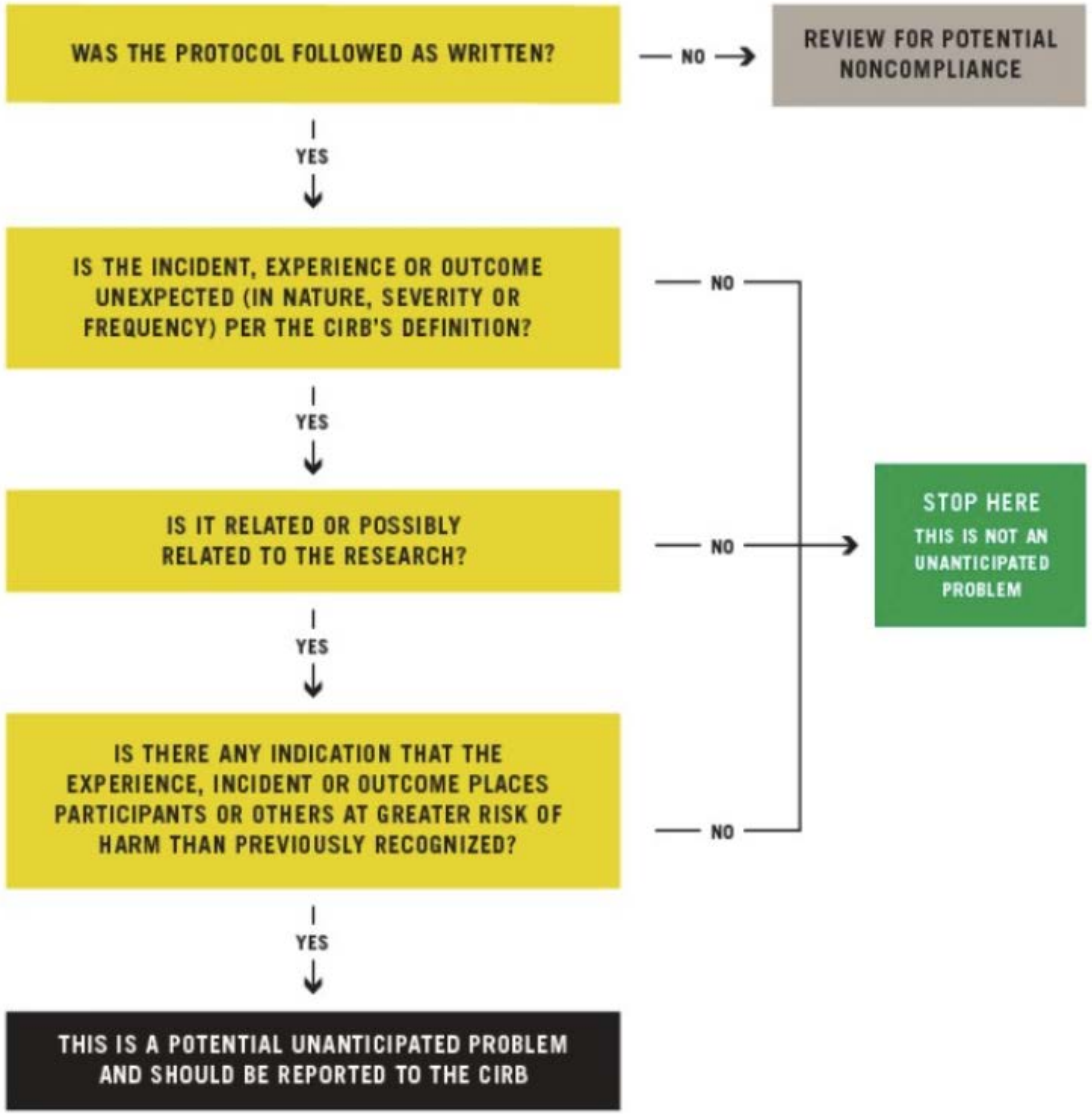
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea Dry mouth		***Diarrhea (Gr 3)*** ***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		

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.

CIRB Algorithm for Potential Unanticipated Problems



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.

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.

Serious Adverse Events - FAQs

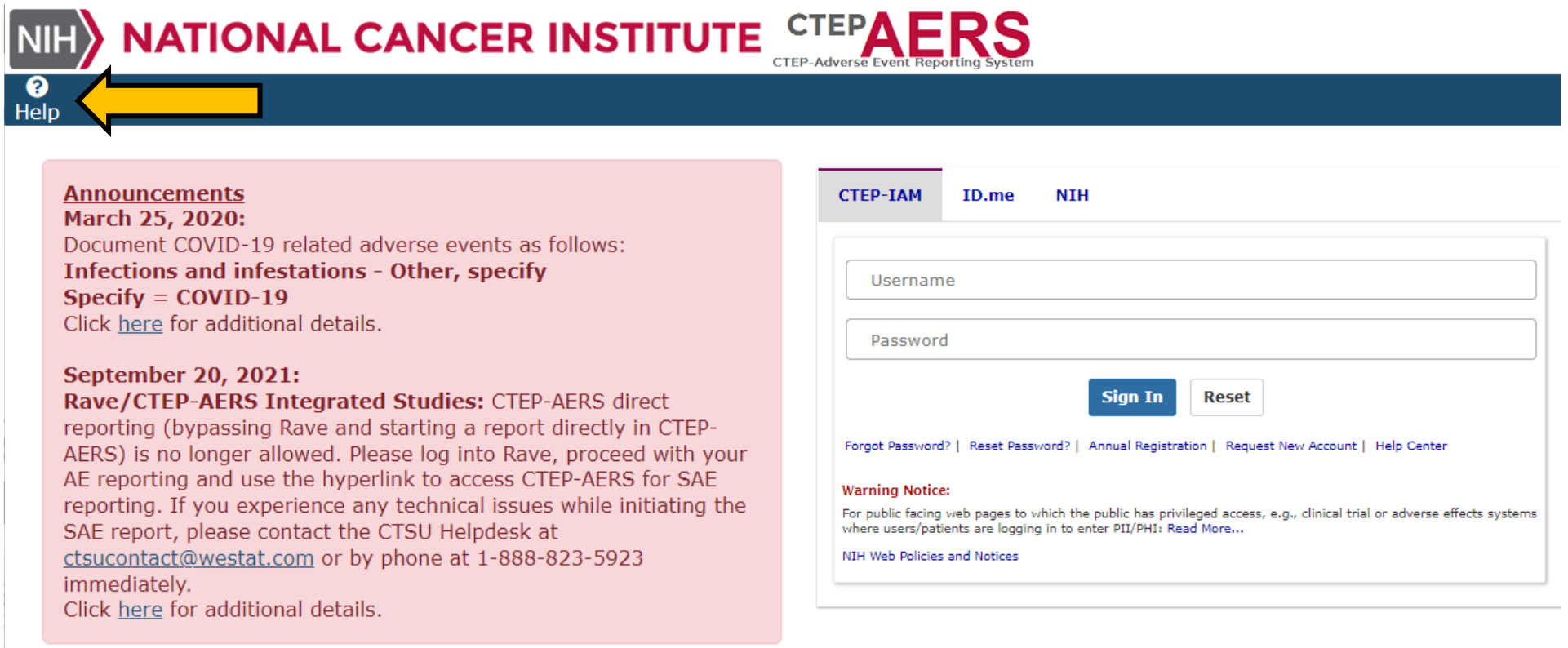
When a patient is on a treatment arm with both investigational and commercial agents, should both the investigational and commercial SAE reporting tables be used to determine reporting timeframes?

- 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.

CTEP-AERS Home Page

Link to CTEP-AERS Home Page



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 6
- 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