Serious Adverse Event Reporting

Kari Williams, RN
Spring 2019

Serious Adverse Event

- SAEs are a sub-set of all adverse events collected.
- The reporting of SAEs is in addition to, and does not supplant, the necessity of adequately reporting adverse events on the data records and in the final results of the clinical trial.

Serious Adverse Events

- As of April 1, 2018, SAEs will be graded using CTCAE 5.0.
- To obtain a copy of CTCAE 5.0 go to ctep.cancer.gov
  - Click on Protocol Development.
  - Choose Adverse Event/CTCAE From the menu.

SAE Reporting Criteria

Consult Section 16.1

SAE Reporting Criteria

- Death
- Life Threatening Event
- Incapacitating Event
- Requires / Prolongs Hospitalization
- Congenital Anomaly
- Other Medically Significant Event

SAE Reporting Tables

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) Other medically important 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 16.10.]

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.

"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

May 6, 2011

Grade 4
Unexpected and Possibly, Probably, or Definitely Related
OR
Grade 5

Table 16.1. Expedited reporting requirements for adverse events experienced by patients [on study arms] [appropriate study arm descriptor] within 30 days of the last administration of the commercial agent(s). [All of the agent(s) used in the study are commercial agents]

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			AdEERS	AdEERS
Possible, Probable, Definite	AdEERS		AdEERS	AdEERS

AdEERS: Indicates an expedited report is to be submitted via NCI AdEERS 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 AdEERS 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.

Section 16.1.f.

16.1 Adverse Event Reporting Requirements

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.

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

- *Thromboembolic events, any Grade regardless of attribution*

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

- *≤ Grade 2 myelosuppression*
- *≤ Grade 4 Infection*

Specific Protocol Exceptions to Expedited Reporting (SPEER)

- SPEER – Section 3.0
- Report AEs on the SPEER **ONLY IF** they exceed the grade noted in the parentheses next to the AE in the SPEER.
- If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Specific Protocol Exceptions to Expedited Reporting (SPEER)

Adverse Events with Possible Relationship to Oxaliplatin (CTCAE 4.0 Term) [n= 1141]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>30%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			*Anemia (Gr 4)*
	Disseminated intravascular coagulation		*Disseminated intravascular coagulation (Gr 4)*
	Febrile neutropenia		*Febrile neutropenia (Gr 4)*
	Hemolysis		*Hemolysis (Gr 1)*
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
	Atrial fibrillation		*Atrial fibrillation (Gr 4)*
	Atrial flutter		*Atrial flutter (Gr 1)*
	Paroxysmal atrial tachycardia		*Paroxysmal atrial tachycardia (Gr 3)*
	Sinus bradycardia		*Sinus bradycardia (Gr 3)*
	Sinus tachycardia		*Sinus tachycardia (Gr 3)*
	Supraventricular tachycardia		*Supraventricular tachycardia (Gr 4)*
	Ventricular arrhythmia		*Ventricular arrhythmia (Gr 4)*
	Ventricular fibrillation		*Ventricular fibrillation (Gr 1*
	Ventricular tachycardia		*Ventricular tachycardia (Gr 1)*

Reporting a Death

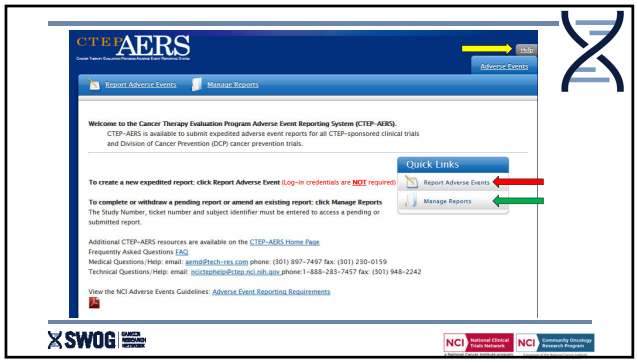
Any death while on treatment or within 30 days of the last dose of study agent must be reported via CTEP-AERS.

Reporting a Death

- Death Attributable to CTCAE Term
- Death, NOS [If it cannot be attributed to a CTCAE term associated with Grade 5]
- Sudden Death NOS
- Disease Progression

Pregnancy Reporting

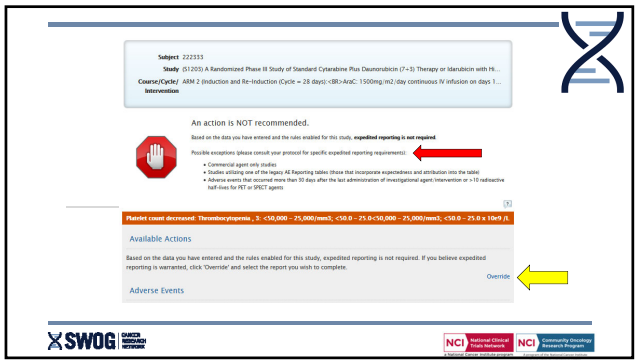
- Refer to Section 16.1 of the Protocol
  - Report via CTEP-AERS
  - NCI Pregnancy Reporting Form
- Pregnancy [Study Participant]
- Pregnancy Loss
- Death Neonatal



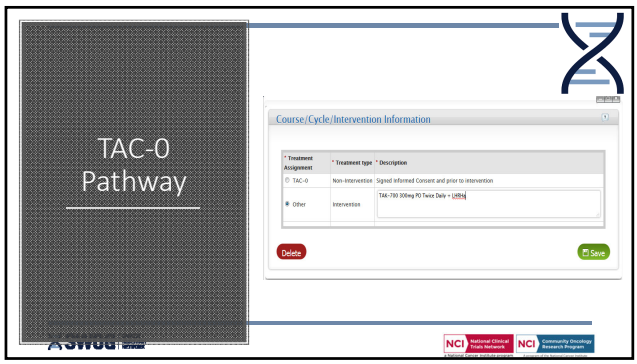
CTEP-AERS Report Pathways

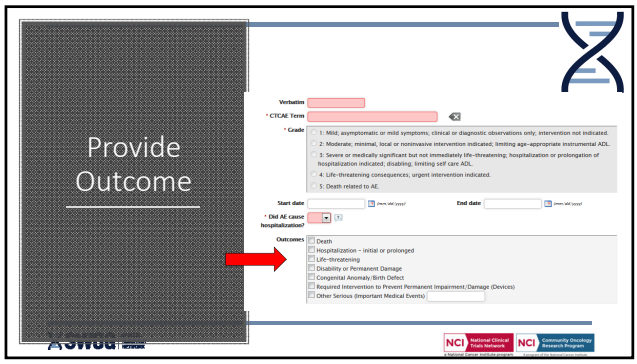
- 24-Hour Pathway
  - 24-Hour Notification Report
  - Complete Report due in five Calendar Days
- 10 Calendar Day Report

**Regardless of pathway the CTEP-AERS system will send reminder emails to you as long as your report remains "pending" in the system.


An action is NOT recommended.
Available Actions
Adverse Events
Override


CTEP-AERS Report Sections
CTEP AERS


TAC-0 Pathway
Course/Cycle/Intervention Information
Delete
Save



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

Attribution Error

For Each Event You Must Provide One Positive Attribution

- The adverse event, 'Infections and infestations - Other: Treating for cellulitis.,' is not attributed to a cause. An attribution of possible or higher must be selected for at least one of the causes.
- Each Adverse Event needs one or more attributions of Possible, Probable, or Definite. An adverse event that resulted in death with AE term Death NOS, Sudden death NOS, Fetal death and Death neonatal is considered exempt from this requirement.

Attribution

- Information entered in any of the following areas will result in an attribution assignment being required:
  - Treatment agent(s)
  - Cancer
  - Concomitant Medication
  - Contributing Cause

CREATING AN AMENDMENT Follow the "One Ticket per Course/Cycle" Rule

Course Information

Start date of first course :	09/02/2016
Start date of course associated with Expedited Report :	03/21/2017
Start date of primary AE :	03/27/2017
End date of primary AE :	
Course Number on which event(s) occured :	8
Total number of courses to date :	8
Was Investigational Agent(s) administered on this Study?:	Yes

Useful Terminology

- A recurrent SAE is one that occurs and resolves during a cycle / course and then reoccurs in a later cycle or course.
- The SAE is reported at the first occurrence, and then reported again if reoccurs at an increased grade or is associated with a hospitalization.

Useful Terminology

- A persistent SAE is one that extends continuously, without resolution between cycle/courses.
- A persistent SAE must be reported only once unless the grade becomes more severe in the same or subsequent cycle/course.

Useful Terminology

- A **secondary malignancy** is a cancer caused by treatment for a previous malignancy.
- A secondary malignancy is not considered a metastasis of the initial neoplasm.

Secondary Malignancy

Report under SOC "Neoplasms benign, malignant, and unspecified" (including cysts and polyps) – CTCAE 5.0

- Leukemia secondary to oncology chemotherapy (e.g., AML)
- Myelodysplastic Syndrome (MDS)
- Treatment-related secondary malignancy

Useful Terminology

- A **second malignancy** (one unrelated to the treatment of a prior malignancy) or metastasis from the initial malignancy are not reported as an SAE.

Routine Reporting Only

Supporting Documentation

SUPPORTING DOCUMENTATON TO BE SUBMITTED TO SWOG OPERATIONS OFFICE WITHIN **FIVE** DAYS.

- This is a separate submission from any documentation sent to NCI/CTEP.
- Submission Instructions will be contained in the email request you will receive from the SAE Program Manager as well as protocol section 16.1.f.

Supporting Documentation

Remember to Protect Patient Privacy When Submitting Supporting Documentation

- PT ID Number
- Protocol Number
- CTEP-AERS Ticket Number
- Coversheet with Total Number of Pages

Date of Discovery

Sites may not be aware of an event at the time it occurs – it is important to document the date the site is aware of an event if different from the dates of events reported on a CTEP-AERS report.

Prior to an Audit

- SAEs Reported Late
- SAEs Reportable to Local Institutional Review Board (IRB)

SWOG SAE Reporting Summary

1. Consider the possibility that any AE could be reportable as an SAE. (Protocol Section 16)
2. If indicated, initiate a CTEP-AERS REPORT within 24 HOURS of the event or discovery of the event. (if unable to access the internet, contact the Operations office)
3. Submit the report within the PROTOCOL-SPECIFIC NUMBER OF CALENDAR DAYS
4. Send SUPPORTING DOCUMENTATION to the Operations office and NCI (as required / requested)

Timely Reporting = Patient Safety & Regulatory Compliance

SWOG SAE Program Contacts

- General email: adr@swog.org
- Kari Williams SWOG SAE Program Manager
  Phone: 210-614-8808 extension 1020
  email: kwilliams@swog.org
- Patti Felts SWOG SAE Coordinator
  Phone: 210-614-8808 extension 1015
  email: pfelts@swog.org

Resources and Support

For Information on CTEP-AERS application
- ctep.cancer.gov
- Click on Protocol Development
- Choose Adverse Event/CTCAE from the menu

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements (September 16, 2013)
- SWOG Policy #23 available on SWOG website

Resources and Support

CTEP-AERS **Medical** Questions / Help:
Email: aemd@tech-res.com
Phone: (301) 897-7497
Fax: (301) 897-7404

CTEP-AERS **Technical** Questions / Help:
Email: ncictephelp@ctep.nci.nih.gov
Phone: 1-888-283-7457 or 301-948-2242


Questions?
SWOG
NCI National Clinical Trials Network
NCI Community Oncology Research Program