

# Fall 2020 SWOG ONCOLOGY RESEARCH PROFESSIONALS OPEN FORUM A Meeting – Virtual

## SUMMARY

**Date:** Thursday, September 24, 2020

**Time:** 2:15 – 3:15 pm CT

### Agenda:

[Welcome](#)

[QA Audit and CAPA Presentation with Q&A](#)

[AE & SAE Presentation with Q&A](#)

[Conclusion and Evaluation Poll](#)

### Welcome

0:00:00

Deb Bergevin welcomed the group.

Noted any Chat questions they cannot get to will be answered and posted on the SWOG website, along with the presentation slides and handouts.

## 2020 Fall ORP Open Forum Session A



**Session Leader:** Deb Bergevin, BS, Quality Assurance Specialist, Seattle Cancer Care Alliance  
SWOG ORP Education Committee

### Agenda:

- 2:15 Welcome
- 2:17-2:45 QA Audit and CAPA presentation with Q&A
- 2:45-3:13 AE & SAE presentation with Q&A
- 3:15 Conclusion & Evaluation Poll

**Session Recordings, Handouts & Slides Available:** [www.SWOG.org](http://www.SWOG.org)

## QA Audit and CAPA Presentation with Q&A

0:00:28

Bergevin introduced Elaine Armstrong, QA manager, SWOG Operations Office, to present on quality assurance (QA) audits, regulatory review, and corrective and preventative actions (CAPAs).

- Bergevin noted Armstrong is the go-to person for QA questions

Also introduced Heather Hillman, senior nurse auditor, SWOG Operations Office, for insights on proper CAPAs.

0:01:01

Armstrong said most in the group know SWOG has moved to remote audits.

- NCI Clinical Trials Monitoring Branch approved these, given travel restrictions
- Said NCI working on SOPs on this that will go out soon
- Armstrong noted the remote procedure is pretty similar to the onsite
  - But all communications through technology
- Regulatory docs emailed or uploaded
  - Not typically privacy concerns with these
- Drug accountability records also emailed or uploaded
- Been doing pharma reviews with videoconferencing

0:02:16

- Armstrong said giving her office access to the site's EMR system is most efficient
  - 1 year earlier most sites would have been unwilling to do this
  - Now about 50%
  - SWOG signs a privacy agreement
- If site doesn't want this approach, needs to upload the records
  - More work for site (and SWOG), but SWOG is flexible
  - Upload options:
    - CTSU Source Document Portal
    - SWOG SharePoint site

## 2020 Fall ORP Open Forum Session A



### Quality Assurance (QA) Audits, Regulatory Review & Corrective and Preventative Actions (CAPAs)

**Presenter:** Elaine Armstrong, MS, QA Manager, SWOG Operations Office, San Antonio, TX  
**Presenter:** Heather Hillman, RN, BSN, ONC, Senior Nurse Auditor, SWOG Operations Office, San Antonio, TX



### Remote audits



- NCI-CTMB has approved/endorsed remote auditing due to travel and visitor restrictions related to Covid-19
- Audit process as similar to on site auditing as possible with communications and exit interview via email, phone or video app
- Regulatory documents emailed or uploaded
- Drug accountability records emailed or uploaded and pharmacy review done virtually via video app



### Remote audits



- Ideally, EMR access given for the patient case review
- If not, patient records are uploaded for review
- Options for uploading documents into a secure portal – CTSU Source Document Portal, SWOG SharePoint site, local site portal
- SWOG has contracted with a company to create an Audit Document Management System within the Office 365 setting to meet our audit needs



- Been having glitches
- Meeting next week to build dedicated audit system in SharePoint
  - Local site portal
- Largest remote audit thus far 25–30 cases
  - Armstrong said she would be reluctant to do remote audit for really large site with 75 or 100 cases
    - None this size on schedule until after first of year

0:04:23

#### COVID-19 deviations

- Paper form provided months ago for sites to record deviations
- Now must be reported in Rave
- Get lots of questions about whether these deviations are major or minor

#### Armstrong provided guidelines

- Variances for protocol requirements that have been officially approved by CTEP are not deviations
  - E.g., shipping investigational agents direct to patients
- If protocol has been revised to extend timeframes (e.g., assessments or submission of data or specimens), those are not deviations and don't need to be reported
- Temporary variances via SWOG memos DO need to be reported
  - Not official protocol changes
- Armstrong reminded group that in almost all cases, deviations won't result in audit deficiency
  - Primarily a way for SWOG to collect important information

#### Reporting Covid-19 Deviations



- Variances from protocol requirements previously approved by CTEP are not considered deviations (e.g., investigational agents shipped directly to patient).
- Some protocols have been revised to provide extended timeframes for assessments and/or specimen and data submission for Covid-19 or other extenuating circumstances. Following these updated timeframes do not need to be reported as deviations.
- Temporary variances distributed via memo from SWOG or the NCI must be reported as a deviation.
- In most cases, deviations will not result in a deficiency during an audit.

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0:06:22

Armstrong provided guidance on specifics:

- Activities performed by a local healthcare provider
  - E.g., patient lives 4 hours away: okay for their labs to be done locally?
  - Not something new; just done infrequently in past
  - Not encouraged, but NCI says okay during COVID
    - Site investigator must still provide direct oversight
  - Examples of things that could be done by a local provider:
    - Labs
    - Imaging
    - Physical exams
    - Treatment with non-investigational agents
    - SoC therapy such as surgery or radiation
      - If no extra credentialing is required
  - These are not deviations
  - But site must have process to submit required information to research site so it can submit data
  - If a local provider is not cooperating after numerous requests, site should cease work with provider

## Reporting Covid-19 Deviations



- Activities performed by a local healthcare provider, if being provided on an intermittent/short-term basis with direct oversight by the Responsible Investigator with respect to protocol requirements and clinical care (e.g., lab tests, imaging, physical exams, treatment with non-investigational agents, other SOC therapy such as surgery or radiation if credentialing is not required) are not considered deviations. Processes must be in place to report required information to the Responsible Investigator who is responsible for ensuring data is submitted in Rave.

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0:08:16

Minor deviations:

- Don't impact patient safety or compromise study data integrity
- SWOG has best practices document that includes windows for labs, treatments, etc.
  - If delay falls within best practices window, not a deviation
- Minor delays in treatment administration, study visits, or follow-up assessments will be lesser deviations
  - E.g., single missed lab or office assessment, or single day of treatment
- Study visits conducted by phone or videoconference are minor deviations

## Reporting Covid-19 Deviations



- **Minor deviations:** do not impact patient safety, compromise the overall integrity of the study data (ability to draw conclusions from the study data)
  - Minor delays are often addressed in the Best Practices document
  - Delays in treatment administration, study visits or follow-up assessments
  - A single missed assessment (i.e., office visit, lab procedure) or a single missed dosing
  - Study visit conducted by phone or video conference

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0:09:13

#### Major deviations:

- Those that could impact patient safety, increase risk, or affect overall data integrity
- NCI has issued guidance:
  - Visits for H&P, performance status, toxicity assessment that are needed to determine eligibility *must* be done in person
  - Failure to follow all eligibility criteria is a major deviation
  - Missed endpoint assessment is a major deviation
  - *Multiple* missed labs or toxicity assessments add up to major deviation
    - Becomes unsafe to keep patient on treatment if site misses assessments for many visits in a row
  - Failure to collect research specimens is a major deviation
    - Unless lab is shut down (some shut down temporarily)
  - Multiple missed visits while patient is on treatment is major deviation
    - More flexibility if patient is already in follow-up

#### Reporting Covid-19 Deviations



- **Major deviation:** impact on patient safety, substantially alters risk to the patient, compromises the overall integrity of the study data
  - Eligibility – no in person visit for H&P, PS, toxicity assessment, if applicable
  - Missed endpoint assessments
  - Multiple missed labs, toxicity assessments
  - Substantial treatment delays
  - Failure to collect research specimens (unless lab is closed)
  - Multiple missed visits while patient on treatment

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0:10:47

#### Armstrong discussed withdrawal of consent.

- Several issues have arisen over past couple of months
- Withdrawal of consent:
  - Patient refuses to participate further in the research and does not wish to have their future medical information collected for research
- If patient says they want to withdraw from study, important to have conversation with them to determine what exactly they want to withdraw from
  - Sometimes patients quit study treatment but are willing to be followed
  - May want to stop treatment but still be willing to come in for follow-up visits
  - May be willing to let their medical data be reported from their chart
  - May be okay with a once-a-year phone call
    - Survival is often an endpoint, so having basic follow-up data is important

#### Withdrawal of Consent



- Withdrawal of consent occurs when the patient refuses to participate further in the research study and does not wish for future medical information to be collected or used for the purpose of research.
- It is important that you determine with the patient whether 1) they no longer wish to be treated per protocol; 2) they no longer wish to be followed per protocol or 3) both. The subject may be willing to allow the investigator to continue some research activities (e.g., follow-up assessments, specimen collection, questionnaires, phone calls for endpoint or survival status) or allow the site to obtain private information from the subject's medical records

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- Very important to determine exactly what patient agrees to
- Also very important to document this in research record
  - Sometimes in audit they see one sentence saying patient withdrew consent with no other information
  - Not then sure whether process occurred as it should have

0:12:38

- If patient withdraws consent, medical records may be accessed consistent with original consent process without additional consent *to obtain information collected prior to subject's withdrawal*
  - If there's a query for site to submit information from time before the patient's consent withdrawal, site can collect and submit that data
  - All information up to withdrawal remains part of study database and can be used in study analysis
  - SWOG has had requests to remove a patient's data from the database:
    - Not allowed to do that
    - FDA states it's acceptable to keep data from before withdrawal
  - *Can* report patient data even after consent withdrawal date if obtained from *publicly available* data source
    - E.g., social security death index
  - Sites sometimes have local guidance on this topic
    - FDA and OHRP say this is okay
  - Have had situations in which site did not want to provide audit data for patient who had withdrawn consent
    - But data up to time of withdrawal stays part of study and is subject to audit
    - Can be very important information in final study analysis
      - E.g., especially for registration study

## Withdrawal of Consent



- Medical records may be accessed consistent with the original consent process, without additional consent, to obtain information collected prior to the subject's withdrawal from the study.
- Data must be submitted, queries addressed, etc. for the timeframe prior to the time of withdrawal.
- The data collected on the subject to the point of withdrawal remains part of the study database, may be used in the study analysis and remains subject to audit.
- Publicly available sources of information to determine a subject's vital status (and if deceased, cause of death) after a subject withdraws from a clinical investigation may be consulted. This activity does not require subject consent because the information is publicly available.

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0:14:47

#### IRB review of closed studies

- Often sites ask to close out study with IRB because site is no longer following patients
  - Patients have completed follow-up or have withdrawn consent
- SWOG policy is that sites should maintain IRB oversight of a study until it is added to “List of Protocols with No Required Follow-up”
  - List is on CRA Workbench
- Important because even though a site is no longer following patients, may be need for clarification or need for additional information
  - If site has closed out study with IRB, it may not be able to submit requested data
- This is particularly important for FDA Registration Studies
  - Submission to the FDA often requires additional analysis with additional data or clarification
  - Site won’t be able to submit that data if it has closed study with IRB
  - Example:
    - FDA does inspection and there is an SAE identified that had not been previously reported
    - Site needs to be able to submit this data

#### IRB Review for Closed Studies



- IRB oversight of a study must continue until the protocol has been added to the List of Protocols with No Required Follow-up (available on the CRA Workbench)
- Even if all patients have completed follow-up activities, are deceased or have withdrawn consent, there may be requirements for further data submission, requests to answer queries, etc.
- This is especially important for FDA Registration Studies because the final study analysis may identify additional data collection or data clarification requirements. In the case of an FDA inspection, it is critical that there are no barriers to the review and preparation of data including data submission and data corrections (e.g., SAE identified that must be reported).

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0:16:32

- Armstrong recognized it can be lot of work to submit for IRB review
  - But if not following patients, nothing to do except keep study open
    - With CIRB, really nothing to do
    - With local IRB, need only continuing review
      - Usually can be done by rolling study over to S9808
      - No need to maintain current consents or process revisions if no patients being followed
  - Exception happened few years ago:
    - Study revised to extend follow-up time
    - Patients had to be reconsented

#### IRB Review for Closed Studies



- Not necessary to maintain a current consent or process revisions if no patients in follow-up
- If a registration study has been closed out at your site, you are highly encouraged to reopen the study for follow-up activities.
  - If using the local IRB, the IRB may conduct expedited review of follow-up activities only.
  - If using the CIRB, submit a Study Specific Worksheet and select "Open New Study" as the reason. You should also add a note to that field indicating that the study was closed prematurely at your site so it is evident to the reviewer that the study had been open previously.

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- Especially for registration studies, if site has already closed study, highly encouraged to reopen the study for follow-up activities
  - For local IRB, site only needs to do expedited review for follow-up activity
  - For CIRB, submit Study Specific Worksheet and select “Open New Study” as reason
    - Then add note indicating that site closed study prematurely so CIRB is aware site had study open previously
    - Getting to final analysis on S1605 and have word that several sites have closed it
      - They had had it open with CIRB
      - Since little to no work to be done at site level, if using CIRB, SWOG doesn’t consider it a burden to site to keep study open

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0:18:39

Armstrong introduced Heather Hillman to present on CAPA responses.

- An area often in need of NCORP guidance



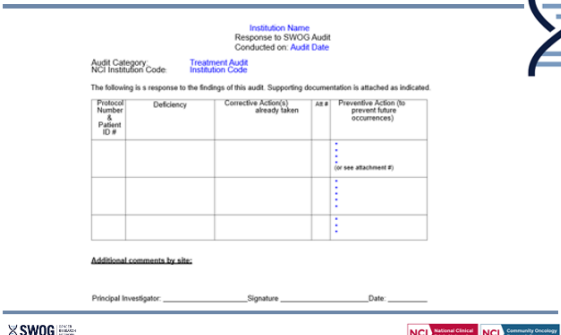
## CAPA RESPONSE OVERVIEW



0:18:57

Hillman said many CAPAs come to them: sometimes happy with them, sometimes not.

- Wanted to review what makes auditors happy and what does not
- Slide displays template sites will receive if they have to respond to audit deficiency
- Said there are multiple versions of this template
  - This is a plain one
  - Site needs to complete areas in blue
- Okay to cut and paste into template
  - With care



The following is a response to the findings of this audit. Supporting documentation is attached as indicated.

Protocol Number & Patient ID #	Deficiency	Corrective Action(s) already taken	As #	Preventive Action (to prevent future occurrences)
				(or see attachment #)

Additional comments by site:

Principal Investigator: \_\_\_\_\_ Signature: \_\_\_\_\_ Date: \_\_\_\_\_

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0:20:01

Hillman said SWOG wants sites to respond to *major* deficiencies only.

- Said she gets calls from sites that cannot tell from a report what it is SWOG wants them to address
  - Example, a major specimen deficiency
    - Located under data quality
  - But several other things also under data quality that are not things SWOG wants them to address




## SAVE TIME AND EFFORT –

### ADDRESS MAJOR DEFICIENCIES ONLY

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0:20:58

- Hillman said sites should look at report to identify major deficiencies to address
- Said she would send them email identifying pages to address
- Said example of CAPA on slide was well done
  - First page has two major eligibilities
  - Approximately same thing
    - Local pathologist signing off on S1400 local pathology review form
  - Under Corrective Actions, even though similar deficiencies, site has identified causes for each



Protocol Number & Patient ID #	Deficiency	Corrective Action(s) already taken	As #	Preventive Action (to prevent future occurrences)
S1400 712345	Major Eligibility: Section 51.1c: The local interpreting pathologist must review and sign off on the S1400 Local Pathology Review Form prior to screening/prescreening registration. The pt was registered on 12/09/10, but the local pathologist did not sign the review form until 12/11/10.	Root cause analysis was performed, and it was discovered that the registering CRA did not obtain the review form signature due to lack of knowledge and human error.		Key CRAs attended the audit exit interview and were reminded of this requirement. A follow-up meeting on 7/20/19 included brainstorming on how to prevent this from reoccurring. The conclusion was a double-check of eligibility criteria prior to registration. In addition, the CRAs will not register pts unless they have both the tissue block and the SIGNED pathology form in hand.
S1400 723456	Major Eligibility: Section 51.1c: The local interpreting pathologist must review and sign off on the S1400 Local Pathology Review Form prior to screening/prescreening registration. The pt was registered on 01/15/2018, but the local pathologist did not sign the review form until 01/16/2018.	Root cause analysis was performed, and it was discovered that the registering CRA had sent the pathologist the form, but didn't receive it back.		Key CRAs attended the audit exit interview and were reminded of this requirement. A follow-up meeting on 7/20/19 included brainstorming on how to prevent this from reoccurring. The conclusion was a double-check of eligibility criteria prior to registration. In addition, the CRAs will notify the pathologist of the deadline for signed form and will not register pts unless they have the signed pathology form in hand.

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- Identified what the problem was
- Under Preventive Actions
  - If site says it will have a meeting to discuss, auditor wants to see a specific date for that meeting
  - If site says data will be reviewed, they want to know timeline
    - E.g., each patient quarterly, 10% of cases
    - Site should be specific about what it will do


0:22:37




- Rest of the CAPA from previous page
- Includes PI signature and date
- Something auditors will review and say “perfect”

S1600A 734567	Major - Protocol-specified research/advanced imaging studies not done or submitted appropriately. The pre-study blood specimens for correlative studies and banking were not submitted. The plasma and buffy coat specimens due at week 3 (04/06/15) were not drawn until week 5 (04/20/15).	Root cause analysis showed that on this occasion one CRA was covering for another, and missed this time point.	CRA's attended the audit exit interview and were made aware that these type of omissions are major deficiencies. During a follow-up meeting, CRA's and research director met to discuss these issues and brainstorm on possible solutions. The CRA's will highlight blood collections on the gt study calendar. When providing coverage, a 2nd CRA will double check the planned orders for the visit and ensure that all specimens are collected appropriately.
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**Additional comments by site:**

Can include comments regarding audit process, suggestions for protocol improvement, site performance goals, etc.

Principal Investigator: Mydoc Rocks, MD, Signature  Date: 8/24/20

SWOG  NCI  NCI 

0:22:59




Which findings are major deficiencies?

- See the assessment of this in review section after all deficiencies are listed
- There is a separate page with the assessment
  - Will usually say “A written response, including a corrective and preventive action plan, must be submitted to address ...”
  - Will then tell you exactly what problem was with deficiency
  - Look for that phrase

**HOW DO I KNOW WHAT FINDINGS ARE MAJOR DEFICIENCIES?**

**\*SEE THE ASSESSMENT COMMENTS FOLLOWING THE REVIEW SECTIONS OF THE REPORT \***

“A written response, including a corrective and preventive action plan, must be submitted to address. . . .”

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0:23:38

#### Common findings: Unnecessary add-ons

- Some common findings auditors don't like to see
- "Errors in submitted data"
- Sometimes there are so many errors that auditors will ask you to address these
- Most times auditor does not want site to address these unless it's specifically requested
- In this example, site addressed things that auditors included in report mostly for educational purposes
  - This happened, and we would like to see it corrected
- In example, site mentioned "re-education of data team"
  - Auditors need dates, who will attend, what content

#### COMMON FINDINGS: Unnecessary add-ons



S1400 723456	Errors in submitted data COMMENTS: The following errors were noted on the Patient and Disease Description Form: The date current staging assessment completed was reported as 4/12/19, but should be 3/9/19. The AJCC M stage was reported as M1b, but should be M1a.	The data was corrected the day of the audit.  The auditor educated the data team regarding the date of staging assessment (day of imaging, not pathology) and the difference between M1A and M1b.	Re-education of the data team will prevent future data entry errors.
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0:24:45

#### Common findings: Copy and paste errors

- Example in which site's major deficiency was blood specimens not submitted
- Site addressed major deficiency but also minor deficiency
  - But as they copied and pasted, put same response under preventive action
  - Does not address deficiency
- This report went back to writers for revision

#### COMMON FINDINGS: Copy & Paste errors



S1400 712345	Protocol-specified research /advanced imaging studies not done or submitted appropriately COMMENTS: The blood specimens for correlative studies and banking, due at registration (3/03/19), were not submitted.	The samples were obtained, but never submitted. The study team was re-educated as to the shipping timeline.	Re-education of the study team will prevent future data entry errors.
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0:25:44

Common findings: Inadequate plan to address deficiency

- Example was major deficiency about local pathology review form not being signed
- Site said specimen form was revised (see slide)
  - Refers to change made in protocol
  - But this was not preventive action plan on site's part
  - Auditors want to know what *site* did
  - Protocols sometimes unclear, but still up to site to fulfill eligibility requirements

COMMON FINDINGS: Inadequate plan to address deficiency			
S1400 712345	Review of documentation available at the time of the audit confirms patient did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol.  COMMENTS: Per Section 5.14, patients must have adequate tumor tissue available, defined as $\geq 20\%$ tumor cells and $\geq 0.2$ mm <sup>3</sup> tumor volume. The local pathology review form states that the specimen has $<20\%$ tumor cells and $< 0.2$ mm <sup>3</sup> tumor volume.	The tissue was sent for central analysis for this patient and was sufficient to assign a study arm.  The specimen form was revised by the sponsor to add the comment "Ineligible" next to the specimen review questions to clarify eligibility expectations.	The specimen form was revised by the sponsor to add the comment "Ineligible" next to the specimen review questions to clarify eligibility expectations.

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0:27:02

Key points

- Address deficiencies
  - Find in comments section of assessment
  - Written action plan is requested
- Keep it short and sweet
  - So auditors don't get things they don't want
  - Saves sites time
- PI must sign completed CAPA

KEY POINTS	
• Address deficiencies as written in the Assessment "Comments"	
• Keep it short and sweet	
• PI must sign completed CAPA	

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0:27:49

Bergevin said there was time for questions.

For Armstrong: How are charts to be color-coded if uploaded?

- Armstrong replied that she had not yet had to work on patient chart that was uploaded
- Asked colleagues if there was way to color code them like paper charts
- Hillman [? 0:28:28] said closest thing they have is first document portal where they have categories
  - Audit folders: treatment, eligibility, inequality

Questions?	
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- Not sufficient right now, but do have color-coded tabs
- Armstrong said when docs are uploaded to SWOG SharePoint, SWOG creates a single folder
  - If NCORP, separate folder for each site
  - Perhaps SWOG should provide more tiered set of folders that say, e.g., eligibility, treatment, labs, ...
  - Might help if SWOG had categories so sites could provide docs by category
- Hillman noted sites make their own breakdown when sending documents
  - Depends on how they have their charts organized
  - If sites label things, auditors can usually figure it out

Bergevin said that was all the time available for questions

- Would post answers to questions not addressed in session

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## AE & SAE Presentation with Q&A

0:30:23

Bergevin introduced Kacie Simpson, assistant director of clinical research operations with U Arkansas for Medical Sciences, and Kari Williams, SWOG's SAE program manager, to present on adverse event (AE) and serious adverse event (SAE) reporting.

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## 2020 Fall ORP Open Forum Session A



### Adverse Event (AE) & Serious Adverse Event (SAE) Reporting

**Presenter:** Kacie Simpson BS, CCRP, Assistant Director of Clinical Research Operations, University of Arkansas for Medical Sciences, Little Rock, AR

**Presenter:** Kari Williams, RN, SAE Program Manager, SWOG Operations Office, San Antonio, TX

**Contributor:** Patti Felts, RN, SAE Coordinator, SWOG Operations Office, San Antonio, TX

0:30:43

Simpson presented on AEs.



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# Adverse Events

Kacie Simpson, B.S., CCRP  
Assistant Director of Clinical Research Operations  
Cancer Clinical Trials and Regulatory Affairs (CCTRA)

0:30:56

Simpson said an AE is any unfavorable or unintended sign, abnormal lab, symptom, or disease temporarily associated with the use of medical treatment or procedure, regardless of whether it's considered related to the medical treatment or procedure.

AEs may also be called side effects, toxicities, adverse experiences, or complications.



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## Adverse Event (AE) Definition


An AE is any unfavorable or unintended sign, abnormal lab, symptom, or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.

AE's may also be referred to as: side effect, toxicity, adverse experience, complication, etc.

0:31:24

Simpson said an AE may be

- Diagnosis
- Sign or symptom
- Disease
- Abnormal lab, vital sign, testing results, or imaging
- Worsening of any pre-existing condition



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## Identifying AE's

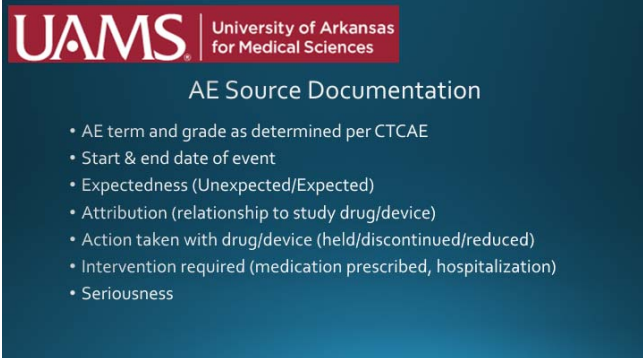
Adverse events may include:

- Diagnosis
- Signs, symptoms, or disease
- Abnormal: labs, vital signs, imaging, ECG results, etc.
- Worsening of any pre-existing symptom or condition

0:31:45

#### AE source documentation

- Items on slide are common data points for AE collection and case report forms
- Protocols that use CTCAE expect AE to be documented using most relevant CTCAE term
  - Start and end date of AE
  - Whether AE was expected per protocol
  - Whether AE was related to study
  - Any action taken due to AE
  - Intervention required
  - Whether AE was serious



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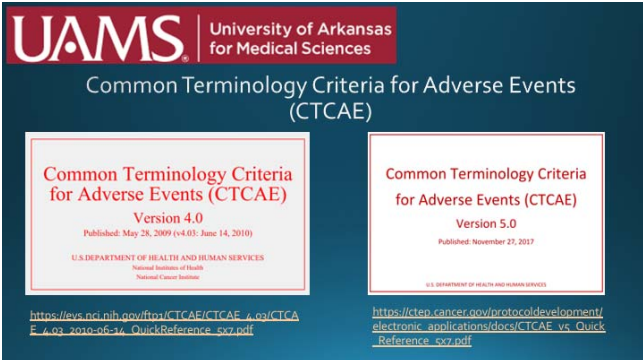
### AE Source Documentation

- AE term and grade as determined per CTCAE
- Start & end date of event
- Expectedness (Unexpected/Expected)
- Attribution (relationship to study drug/device)
- Action taken with drug/device (held/discontinued/reduced)
- Intervention required (medication prescribed, hospitalization)
- Seriousness

0:32:32

#### Common Terminology Criteria for Adverse Events (CTCAE)

- Used for coding AEs
- Version 5 is current version
  - Some older protocols still require AEs under previous version 4.0.03
  - Refer to protocol to determine version required
- Simpson highly recommended downloading the PDF of CTCAE
  - Will allow searching to find correct CTCAE term
- Saw on CTSU website recently that NCI is preparing for new version of CTCAE
  - Version 6 coming fall 2022
  - NCI asking for our input on changes
  - Check CTSU website for info



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### Common Terminology Criteria for Adverse Events (CTCAE)

**Common Terminology Criteria for Adverse Events (CTCAE)**  
Version 4.0  
Published: May 28, 2009 (v4.03: June 14, 2010)  
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health  
National Cancer Institute

[https://evs.nci.nih.gov/ft/ct/CTCAE/CTCAE\\_v4.03/CTCAE\\_v4.03\\_2010-06-14\\_QuickReference\\_csr.pdf](https://evs.nci.nih.gov/ft/ct/CTCAE/CTCAE_v4.03/CTCAE_v4.03_2010-06-14_QuickReference_csr.pdf)

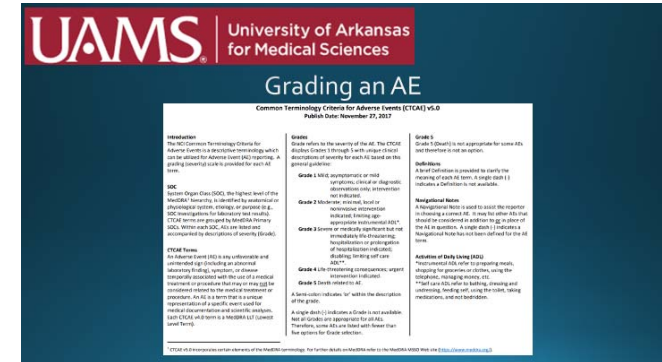
**Common Terminology Criteria for Adverse Events (CTCAE)**  
Version 5.0  
Published: November 27, 2017  
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

[https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_QuickReference\\_csr.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_QuickReference_csr.pdf)

0:33:42

## Grading an AE

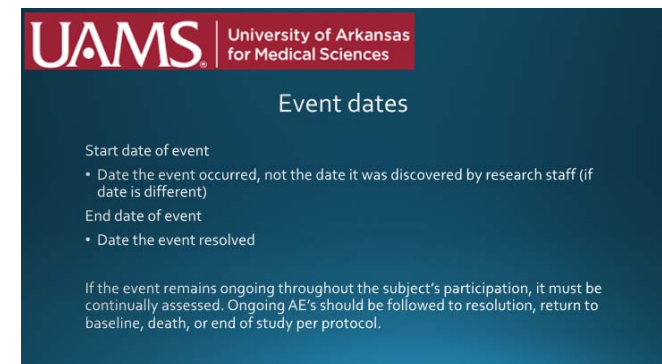
- Second page of CTCAE provides overview on selecting an AE term and grading
- Simpson suggested that if list does not provide term that accurately describes an AE, user can refer to appropriate body system
  - Then select “other” and define AE term
- Lab AEs tend to have result ranges
- Non-lab AEs graded on clinical assessment



0:34:22

## Event dates

- Need to document start date of event
- If subject is unsure, ask them for best guess
  - Ask if they know month or year AE began
- If event remains ongoing, should be continually assessed for improvement, worsening, or resolution
- If AE is resolved, resolution date should be documented
- AEs are followed until
  - Resolution
  - Return to baseline
  - Death
  - End of study per protocol






0:35:13

### Expectedness

- Unexpected AEs are
  - Those not listed in marketed drug labeling
  - Those more severe than indicated in labeling
  - Those not consistent with information in protocol, investigator's brochure, or consent form
  - Those that occurred within class of drugs but not specifically the investigational product



### Expectedness


An unexpected AE is defined as:

- For studies that use marketed drugs/devices
  - An AE that is not listed in the drug's current labeling, or
  - An AE that is more severe or specific than indicated in the labeling.
- For studies that use investigational new drugs
  - An AE that is not consistent with the information about the drug's risks that appears in the protocol, Investigator's Brochure, and consent
  - An AE that is greater than the risk information provided for the drug
  - An AE that has occurred within a class of drugs, but not specifically the investigational product

0:35:41

### Attribution

- AE attribution describes relationship of study intervention to AE
- Attribution typically documents relation to intervention as
  - Unrelated
  - Unlikely
  - Possible
  - Probable
  - Definite



### Attribution


The attribution describes the relationship of the study product/device with an adverse event. Attribution is generally documented using the following:

Attribution	Description
Unrelated	The AE is clearly <b>NOT</b> related to the intervention
Unlikely	The AE is <b>doubtfully related</b> to the intervention
Possible	The AE <b>may be related</b> to the intervention
Probable	The AE is <b>likely related</b> to the intervention
Definite	The AE is <b>clearly related</b> to the intervention

0:36:03

### Action taken

- Important to document action taken with study intervention or if intervention was needed
- Actions include
  - Dose delays
  - Holds
  - Modifications
  - Discontinuations
- ... of study intervention
  - Medication prescribed



### Action Taken/Intervention Needed

**Action Taken**

- It is important for research staff to document the action taken with the drug or device. Examples include: dose modifications, dose delays, dose hold, discontinuation of study therapy/use of device.

**Intervention Needed**

- It is also important to document interventions required to improve AE's. Examples include: medications prescribed (as allowed per protocol), hospitalization, testing ordered, etc.

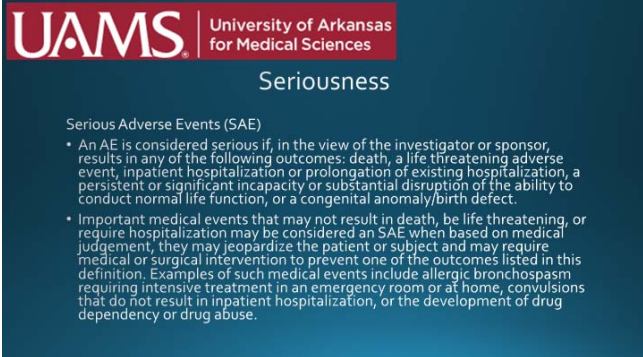
- Test ordered
- Hospitalization required

0:36:30

#### Seriousness

- Very important to document seriousness of AE
- AE considered an SAE if
  - If it is life threatening, requires hospitalization, or prolongs hospitalization
  - If it persistently or significantly disrupts the ability to conduct normal life functions
  - If it results in a congenital anomaly or birth defect
  - Or if it results in death
- AEs that may require medical or surgical intervention to prevent one of the indications above may also be considered SAEs
- Examples of SAEs include
  - Allergic reactions
  - Convulsions
  - Development of drug dependency and abuse

Simpson noted presenter Kari Williams would discuss SAEs in more detail.



The slide features the UAMS logo in the top left corner. The title 'Seriousness' is centered at the top. Below the title, the text 'Serious Adverse Events (SAE)' is followed by two bullet points defining SAEs.

**UAMS** | University of Arkansas  
for Medical Sciences

### Seriousness


Serious Adverse Events (SAE)

- An AE is considered serious if, in the view of the investigator or sponsor, results in any of the following outcomes: death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life function, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when based on medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

0:37:32

#### Tips for reported AEs

- Review AE reporting requirements for all protocols, as they may differ by protocol
  - Some protocols collect from the time of consent
  - Others collect from the start of intervention
- Determine whether all AEs are collected or just those of a certain grade or relationship to intervention
- Is an event medical history or an AE?
  - Events ongoing at time of consent are medical history
  - However, if event worsens while patient is on study, that becomes an AE
  - Simpson noted her site documents medical history using CTCAE terminology and grading at time of consent
    - Makes it much easier to document if event worsens
  - Example: Patient enters study with grade 1 hypertension managed by diet and exercise
    - While on study, patient's hypertension worsens and medication is prescribed to control it
    - This increases the grade to grade 2
    - Grade 2 hypertension becomes an AE




### Tips for Reporting AE's

- Review the AE reporting guidelines for each protocol as they may differ slightly.
  - Examples: Some protocols collect AE's from time of consent and other collect from day of study/intervention; some protocols collect all AE's and others have a minimum grade threshold for reporting.
- Medical events ongoing at the time of consent are not AE's, they are medical history. However, if these medical events worsen while on study they should be documented as AE's.
  - Note: Documentation of medical history using CTCAE terminology and grading at the time of consent make it easier to appropriately capture if/when medical history worsens and becomes an AE.
  - Example: Subject enters study with hypertension that is managed by diet and exercise (Grade 1). While on the trial, the subject's blood pressure worsens and medication is prescribed to control hypertension (Grade 2). Hypertension now becomes an AE.

0:39:06

#### More tips

- Most case report form (CRF) systems require an additional entry when an AE grade changes
  - To record this, must first resolve initial AE
  - Then use date next grade begins as resolution date for initial AE
- Best to report using a diagnosis CTCAE terms rather than listing all of the symptoms, if possible
  - Example:
    - Subject complains of sinus congestion, sneezing, runny nose, and cough



### Tips for Reporting AE's

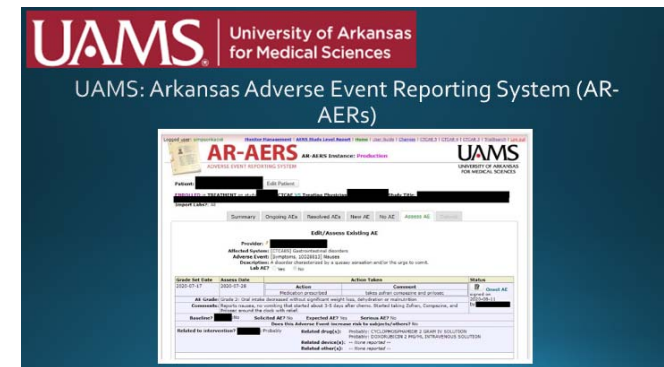
- In most case report form (CRF) systems, if an AE grade changes an additional line entry is needed on the AE CRF. The initial grade would resolve the date the next grade begins.
- Report using diagnosis CTCAE terminology, rather than symptoms, where applicable.
  - Example: Subject complains of: sinus congestion, sneezing, runny nose, and cough. Per CTCAE V5, it would be most appropriate to document Allergic rhinitis, described using the following symptoms: sneezing, nasal congestion, rhinorrhea, and itching. Cough would be listed separately as an AE.
- Death itself is generally not an accepted CTCAE SAE term—the cause of death should be reported using Grade 5.

- Per CTCAE version 5, would be documented as allergic rhinitis, which is described using all of those terms
  - However, the cough is not part of that description for allergic rhinitis
    - Thus, that would be listed as a separate AE term
- Death is generally not an accepted CTCAE term
  - Cause of death should be reported, using grade 5 where applicable

0:40:23

Screenshot of UAMS AE reporting tool: Arkansas Adverse Event Reporting System (AR-AERs)


- System allows documenting all components of AEs and SAEs discussed above
- Is 21CFR-11 compliant
- Has audit trail
- Investigators can review, edit, enter, and sign off here
- Able to give view-only access to monitors and auditors so they can review AEs
- Using this system to collect all elements of AEs has drastically reduced paper usage in office
- Also reduced number of queries
  - Simpson said in previous system they collected basic information in EMR and would have to find physician to get additional AE information
  - Current system allows all to be captured in one location



0:41:37

#### Resources

- Simpson said the slide contained helpful links she found in preparing presentation
- Believed these would be provided in a handout




### Helpful Resources

- [https://crawb.crab.org/txwb/CRA\\_MANUAL/Vol1/chapter%2013\\_Serious%20Adverse%20Events.pdf](https://crawb.crab.org/txwb/CRA_MANUAL/Vol1/chapter%2013_Serious%20Adverse%20Events.pdf)
- <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32>
- <https://gcp.nidatrainig.org/modules/4/pdf>
- [https://ccrod.cancer.gov/confluence/download/attachments/73041052/AE\\_UP6.pdf](https://ccrod.cancer.gov/confluence/download/attachments/73041052/AE_UP6.pdf)
- <https://www.fda.gov/media/72267/download>
- [https://ccrod.cancer.gov/confluence/download/attachments/73041052/AE\\_UP6.pdf](https://ccrod.cancer.gov/confluence/download/attachments/73041052/AE_UP6.pdf)

0:41:57

Kari Williams presented on SAE reporting.



## Serious Adverse Event Reporting

Kari Williams RN  
SAE Program Manager, SWOG


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0:42:05


Williams said that when collecting AEs, sites always want to be reviewing to identify those that are also SAEs.

- SAEs are subset of AEs



## Serious Adverse Event

- SAE's are a sub-set of all adverse events collected.
- The reporting of SAE's 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.



Adverse Events

Serious Adverse Events

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0:42:30

#### SAE reporting criteria

- Protocol section 16.1 or section 8 will have SAE recording criteria
- Move of these criteria to section 8 is recent
  - So for now will have protocols with both
- Will find guidance there for using Rave/CTEP-AERS Integration to record SAEs, if it applies to protocol
  - Does for most new protocols
- Will include tables for general reporting criteria
- Williams said users would also want to carefully review it for additional subsections that list exceptions
  - Sometimes for things that don't need to be reported through expedited reporting
- Will also list AEs of special interest
  - Often regardless of grade or attribution these are to be reported on expedited reporting form

0:43:43

#### Changes

- Reporting is changing
- Older protocols allow going just to CTEP/AERS to report
- Newer protocols use integrated system
  - Start in Rave
  - Complete appropriate AE form for appropriate treatment cycle
    - It then moves all that information to CTEP/AERS system to finish report



#### SAE Reporting Criteria Section 16.1 OR 8.0

- Guidance for reporting using the Rave/CTEP-AERS Integration
- Tables containing reporting criteria
- Additionally there may be subsections
  - Events that are Adverse Events of Special Interest (AESI)
  - Adverse Events that are exceptions to expedited reporting.

It is important to read through the entire section so you are aware of all the reporting criteria

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#### SAE Reporting is Changing

- SAE Reporting is done by electronically by submitted a CTEP-AERS report which is accomplished:

By directly reporting in the CTEP-AERS system

OR

By utilizing the Rave/CTEP-AERS integration

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0:44:21

## Pathways

- Williams reminded group of 2 reporting pathways
  - 24-hour pathway
    - Creates 2 reports
    - First is 24-hour notification
      - When submitted, creates copy of report due in 5 calendar days
      - Allows you to report information rapidly and complete details as they are available
      - If you don't complete both reports, it will drop out of system as unsubmitted and will take everything with it
  - Regular 10-day calendar report
- For both pathways, system sends emails reminding you of reports pending
  - Once a report times out of system, it can't be retrieved
  - Would have to start over

0:45:43

## SAEs are reported using version 5 of CTCAE

- Version loaded in CTEP/AERS system
- No need to choose it
- In some older protocols, may have AEs in older version
- But all SAEs reported in version 5

## 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.**

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## 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](http://ctep.cancer.gov)
  - Click on Protocol Development.
  - Choose Adverse Event/CTCAE From the menu.

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0:46:16

## Attribution

- Table reiterates assignment of attribution
- PI will be doing this with all information you provide

## Assign an Attribution

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

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0:46:29

## When to create amendment vs a new report

- Follow NCI guidance: One ticket per course or cycle of treatment
  - If you submitted a report and patient has another SAE but you know you've already submitted a report, always refer back
  - Want to look at the start date of the course you associated last report with
  - If same course or cycle of treatment, simply amend that report
  - True even if it is another admission for something completely different
  - Will all be consolidated in one ticket

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) occurred : 8  
Total number of courses to date : 8  
Was Investigational Agent(s) administered on this Study?: Yes

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## Don't forget resolution

- Should provide resolution on SAE report whenever possible
- Always make sure to circle back and update
- Provide end dates for events, if you can
  - Sometimes there is not an end
- Give any follow-up information
- Update subject status
  - Good practice and will save you work
  - Updating it years down the road can be difficult

## Don't Forget to Provide a Resolution

For each CTEP-AERS report submitted you want to make sure that you update the report to provide resolution for the event(s) reported.

As Appropriate:

- Provide End Date
- Update Event Description with any Follow-Up information
- Update Subject Status

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0:48:17

#### Documentation

- For protocols requiring documentation for review, you will get email from either Williams or Patti Felts
  - After they review your report and complete submission they will send email requesting supporting documentation
- They try to tailor it to make clear what they're asking for
- But it is any clinical information you have that supports the report you submitted
- They supply you with contact information to send it to

#### Supporting Documentation



SUPPORTING DOCUMENTATION 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



0:48:58

- Remember to put patient ID, protocol number, ticket number, cover sheet (to indicate number of pages)
  - Include first page of report so they can be sure to associate documentation with right report

#### 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



0:49:30

### Summary of SAE reporting

- As you collect AEs, consider SAEs
- Consult protocol
- Report as indicated
  - 24-hour or 10 calendar day
  - Good idea to report within 24 hours of learning of SAE
  - They understand that sometimes you don't know right away
  - They look at date you were first aware
  - But you want to start report within 24 hours
  - Get submitted ASAP
- Send supporting documentation as quickly as possible so report can be reviewed

### SWOG SAE Reporting Summary



1. Consider the possibility that any AE could be reportable as an SAE.
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



0:50:33

### Questions

Bergevin relayed questions.

For Simpson:

Are concomitant medications considered "intervention"? If so, should the intervention box be checked on the CTEP-AERS CRF if already entered as a concomitant medication?

- Simpson said her gut response was yes, as it would tie AE to con-med prescribed for that specific event

Is the AE program something UAMS created or is it based through a tech company?

- Simpson replied it's a UAMS program

Will all slides be available after webinar?

- Bergevin said yes, would be posted to SWOG website

Bergevin said these were all the AE/SAE questions, so she wanted to return to remaining questions on audits and CAPAs.

## Questions?



Are uploaded documents still de-identified since they wouldn't be if the audit was on site?

- Armstrong said CTSU audit source document portal asks sites to de-identify data
- CTSU system will do it for you, but she's not sure how well that works
- Said technically they don't have to be de-identified, if they're in secure portal, because SWOG auditors have permission to have access to that data
- However, most sites have policies requiring it
- If site doesn't require it, SWOG doesn't

Has SWOG been presented with the EPIC CareLink contract by any sites? Is this something SWOG is willing to sign?

- Armstrong did not know answer, but thought there was a good chance they have
- Said most remote audits are for registration studies
  - Most nurse auditors working alone on those audits
  - They are the ones that have signed most contracts
- Armstrong has been involved in only 2 remote audits
- But they have access to Epic for many cases
- Simpson noted that her site uses Epic CareLink
  - Believed her Lung-MAP studies have used it for auditing
- Armstrong said this makes her suspect they have signed it

Are temporary allowances that impact eligibility criteria major or minor deviations?

- Armstrong replied this was in reference to memos
- Those spelled out in those memos as temporary allowances would be minor
- Versus blatantly not meeting criteria

Bergevin read out a submitted question about patients lost to follow-up:  
How many times should we contact a patient (without successfully contacting them) before we consider them as lost to follow-up?

- Armstrong said response to this is posted on CRA Workbench
  - She believed it is 4 times, but not certain
  - CRA Workbench has "lost to follow-up" link
-

Any suggestions for methods of trying to contact patients?

- Armstrong suggested questioner ask that of someone at another site who would have more experience with that

For CAPA, can reeducation alone be preventive action plan?

- Armstrong said it depends
  - For audits that go well in which there's only one major deficiency, this might be an appropriate response
  - But for something that had occurred multiple times, this would not be sufficient

Bergevin read some comments from the Chat.

(Re: upload of redacted information to SWOG website for remote audit:)

Tiered folders would save sites time for creating their own. Most sites don't have electronic patient charts and would be starting from scratch.

- Armstrong said was good to know
- Would have call tomorrow on updating auditing SharePoint site and would bring up this point

Bergevin read out a tip:

There are some good apps for CTCAE grading in searchable mobile format.

Bergevin thanked presenters, attendees, and IMS techs.

- Reminded attendees to check SWOG website for slides, handouts, and answers to Chat questions
-

## Conclusion and Evaluation Poll

0:58:51

Bergevin asked attendees to complete the evaluation poll (shown below).

### ***Open Forum Poll Questions for Session A:***

- *Overall, the QA Audit and CAPA topics are applicable to my current work.*  
*1 = strongly agree 2 = somewhat agree 3 = somewhat disagree 4 = strongly disagree*
- *The presenters were effective and knowledgeable about the topics.*  
*1 = strongly agree 2 = somewhat agree 3 = somewhat disagree 4 = strongly disagree*
- *Overall, the AE and SAE Reporting topic is applicable to my current work.*  
*1 = strongly agree 2 = somewhat agree 3 = somewhat disagree 4 = strongly disagree*
- *The presenters were effective and knowledgeable about the topics.*  
*1 = strongly agree 2 = somewhat agree 3 = somewhat disagree 4 = strongly disagree*
- *What topics would you like to see at future Open Forums? (Open text field)*
- *Additional Comments: (Open text field)*

0:59:10

Meeting adjourned.

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Please complete  
the Evaluation Poll  
before exiting.



Thank you for your input!

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