Adverse Event Reporting

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Definition of Adverse Event

***An adverse event** is any unfavorable and unintended change in a patient's condition from the day protocol treatment began, regardless of cause.*

An Adverse Event may be…

- **A new event** which was not pre-existing prior to initiation of study treatment
- **A pre-existing event which recurs** with increased severity (grade) or increased frequency following study drug administration
- An event present at the time of study drug administration which is **exacerbated** following initial study drug administration

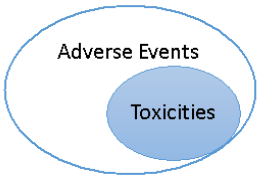
Adverse Event (AE) Reporting: Outline

- Definitions and Background
- SWOG Protocols and adverse events
- NCI Common Terminology Criteria for Adverse Events (CTCAE)
  - CTCAE grade (severity)
  - Attribution
  - Status code
- Online Data Submission: Adverse Events

Adverse Event versus Toxicity

*A **toxicity** is an adverse event considered related or possibly related to the study drug or intervention.*

Both terms may be used in SWOG protocols depending on the context; however, **patient assessments and reporting should encompass the broader category of adverse events.**



Definitions and Background

What are some of the Examples of Adverse Events?

- Nausea or vomiting caused by study treatment
- Worsening of allergic rhinitis from seasonal allergies
- Wrist fracture due to fall
- Abnormal lab result that was not present at baseline
- Increasing tumor pain
- COVID-19 infection and related symptoms

Unless otherwise specified, **all grades of adverse events** (1-5), including abnormal laboratory findings, **must be reported** on the study's Adverse Events Form (AE Form) regardless of clinical significance or attribution to protocol treatment.

Serious Adverse Events (SAEs)

*A **Serious Adverse Event (SAE)** is an unexpected or severe reaction to protocol treatment.*

Example of Dose Modifications

Dose Modifications – Talazoparib (BMN 673)

Dose modifications should be made based on the observed toxicity, as summarized in the tables below.

DRUG	DOSE LEVEL	DOSE
Talazoparib BMN 673	Full	1000 mcg/day
	-1 Level	750 mcg/day
	-2 Level	500 mcg/day
	-3 Level	250 mcg/day
	-4 Level	Discontinue

Table 1: Renal Impairment Dose Modifications

Toxicity	Dose Modification
Grade 3	No hold on treatment required, treatment may continue at next lower dose
Grade 4	Hold protocol treatment until resolution to ≤ Grade 2, treatment may then resume at the next lower dose

AE Information in SWOG Protocols

Protocol Section 9.0 – Study Calendar

9.0 STUDY CALENDAR

	Screening	Baseline Randomization Step 2	Treatment					Off Tx Pre-progression follow-up	Off Tx Post progression follow-up
			Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent cycles		
PHYSICAL									
History & Physical Exam		X	X	X	X	X	X	X c	X c
Weight & Zubrod Performance Status		x	x	x	x	x	X		
Disease Assessment		x			x		X c	X c	
Disease Abnormality Assessment		x							
Toxicity Assessment		X	X	X	X	X	X	X c	X c

c Toxicity assessment must continue until 30 days after the last dose of protocol treatment or until resolution of all acute adverse events, whichever is later.

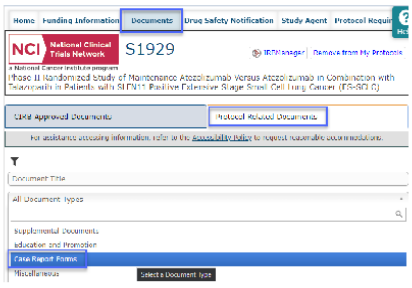
- Assessments required where X is present
- Refer to study calendar footnotes for additional details
- Report all AEs through the end-of-cycle assessment
- "Late Adverse Events" may be captured during follow-up

Relevant Protocol Sections

Section #	Section Name
3	Drug Information
8	Toxicities to be Monitored and Dosage Modifications
9	Study Calendar
14	Data Submission Schedule
16	Ethical and Regulatory Considerations

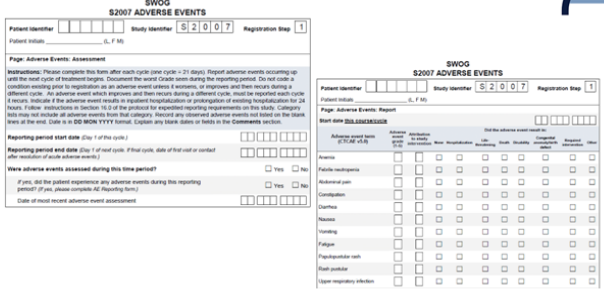
...and don't forget the Master Forms Set in CTSU!

Master Forms Set (All CRFs)



- Available via CTSU (Document Type = Case Report Forms)
- Contains **all** case report forms for a particular protocol, including those used to report adverse events

Master Forms Set (All CRFs)


SWOG
S2007 ADVERSE EVENTS

Patient Identifier | Study Identifier S 2 0 0 7 | Registration Step 1

Patient Initials _____ (L, F M)

Page: Adverse Events: Assessment

Instructions: Please complete this form after each cycle (one cycle = 21 days). Report adverse events occurring up until the next cycle of treatment begins. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens, or improves and then recurs during a different cycle. An adverse event which improves and then recurs during a different cycle, must be reported each cycle it recurs. Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for 24 hours. Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study. Category lists may not include all adverse events from that category. Record any observed adverse events not listed on the blank lines at the end. Date is in **DD MON YYYY** format. Explain any blank dates or fields in the **Comments** section.

Reporting period start date *(Day 1 of this cycle.)*

Reporting period end date *(Day 1 of next cycle. If final cycle, date of final visit or contact after resolution of acute adverse events.)*

Were adverse events assessed during this time period? ☐ Yes ☐ No

If yes, did the patient experience any adverse events during this reporting period? (If yes, please complete AE Reporting form.) ☐ Yes ☐ No

Date of most recent adverse event assessment

SWOG
S2007 ADVERSE EVENTS

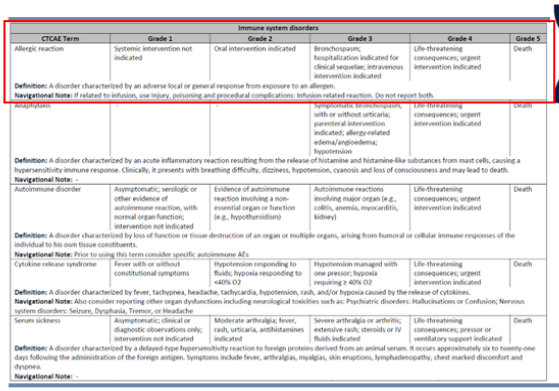
Patient Identifier | Study Identifier S 2 0 0 7 | Registration Step 1

Patient Initials _____ (L, F M)

Page: Adverse Events: Report

Start date this courtesycycle

Adverse event term (CTCAE v5.0)	Adverse event grade (1-5)	Attribution to study rx	None	Hospitalization	Life-threatening	Death	Disability	Congenital anomaly/birth defect	Required intervention	Other
			Did the adverse event result in:							
Anemia										
Febrile neutropenia										
Abdominal pain										
Constipation										
Diarrhea										
Nausea										
Vomiting										
Fatigue										
Papulopustular rash										
Rash pustular										
Upper respiratory infection										


Immune system disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Navigational Note: If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Navigational Note: -					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
Navigational Note: Prior to using this term consider specific autoimmune AEs					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					
Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
Navigational Note: -					

Reporting Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE)

Reporting Adverse Events: CTCAE Terms

- CTCAE terms might not always be listed the way that you expect. Below are some examples of common AEs and their appropriate CTCAE v5.0 term:

  Pneumonia → **Lung infection**

  Thrombocytopenia → **Platelet count decreased**

  Shortness of breath → **Dyspnea**

- Each system category includes an "Other, specify" option in the rare case there is no term is available for an adverse event. Please use "other" sparingly!

NCI Common Terminology Criteria for Adverse Events (CTCAE)

- CTCAE versions and other AE reporting resources are found at ctep.cancer.gov
  - Version 5.0 published in November 2017
    - Used for all SAE reporting (April 2018 to present)
    - Used for routine AE reporting for newer SWOG protocols
- Some studies may use a different CTCAE version for routine AE reporting vs. SAE reporting.

Reporting Adverse Events: COVID-19

- Document COVID-19 infection as an adverse event as follows:
  - CTCAE Term = **Infections and infestations - Other, specify**
  - Specify = **COVID-19**
- Report any other AEs that the patient experiences
- If applicable, report via CTEP-AERS

Additionally, the following trials also require the first positive COVID-19 test to be reported on the COVID-19 Diagnosis form in RAVE:

S1418, S1501, S1826, S1918, and S1925

Blood and lymphatic system disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements. **Navigational Note:** -					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. **Navigational Note:** -					
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. **Navigational Note:** -					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction. **Navigational Note:** -					

Additional AE Data Collection Items

Some additional data items may be collected for AE reporting purposes:

- Serious?
- Hospitalization?
- Is the AE immune-related?
- Onset date
- Resolution date
- Ongoing?
- Action taken with study drug
- Outcome of AE
- Treatment received for AE?

Reporting Adverse Events: Attribution

The attribution code describes, **in the opinion of the investigator**, how likely it is that the adverse event is due to protocol treatment:

Relationship	Attribution	Description
Unrelated to Inwestigational Agent/Intervention	**1**- Unrelated	The AE is *clearly not* related to the intervention
	2- Unlikely	The AE is *doubtfully* related to the intervention
Related to Inwestigational Agent/Intervention	**3**- Possible	The AE *may be* related to the intervention
	4- Probable	The AE is *likely* to be related to the intervention
	5- Definite	The AE is *clearly* related to the intervention

Online Data Submission

Adverse Events

Reporting Adverse Events: Status Code

Some SWOG studies will collect **status** in addition to grade and attribution. The status code describes the state of the adverse event at various points throughout the study.

Status Codes range from 1 to 3:

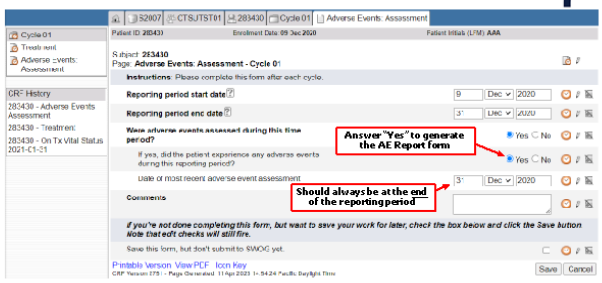
1 = New
2 = Continues at same or lower grade
3 = Increased grade OR improved then worsened

Online Data Submission: Adverse Events

SWOG has two EDC systems in use:

- CRA Workbench (legacy trials only)
- **Medidata RAVE**

Online Data Submission: Adverse Events



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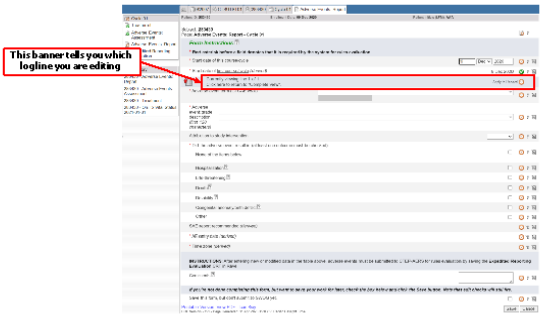

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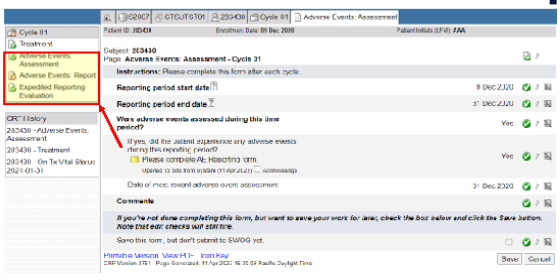

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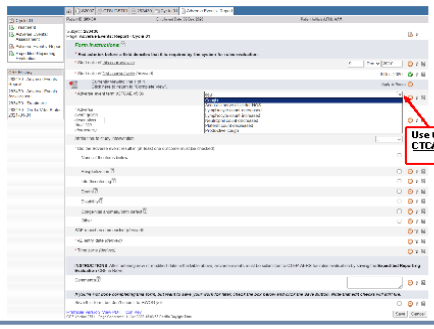

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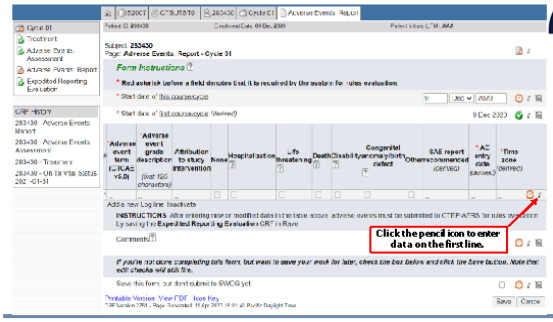

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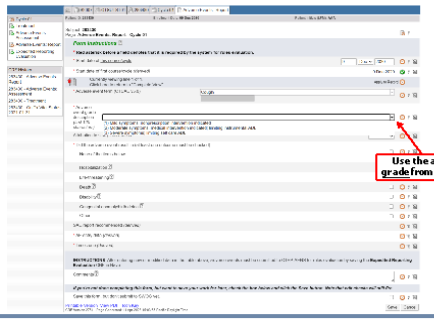

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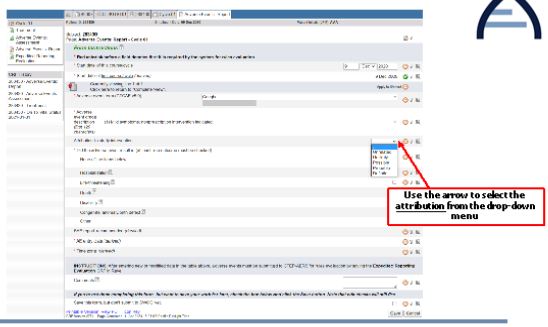

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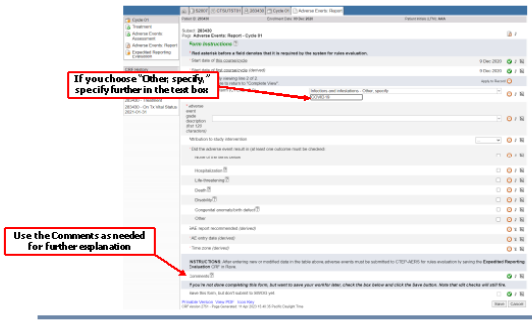

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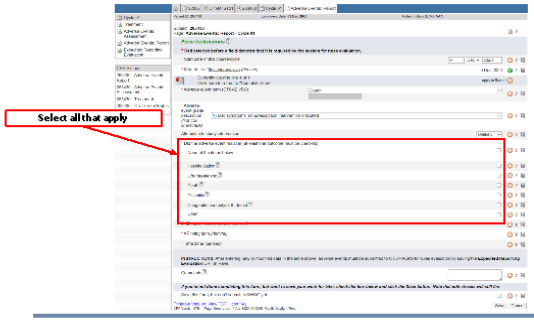

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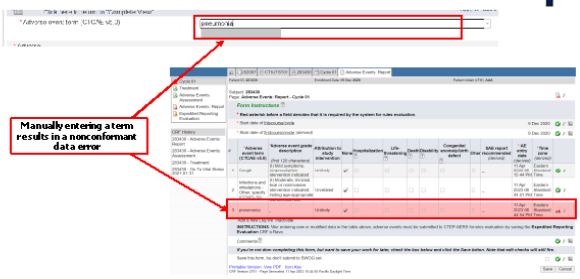

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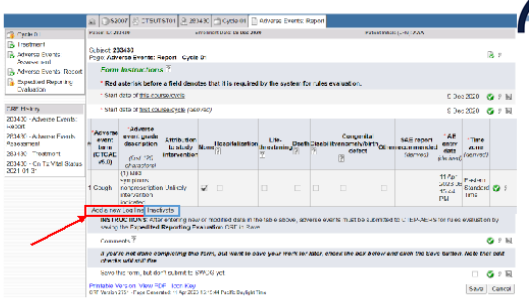

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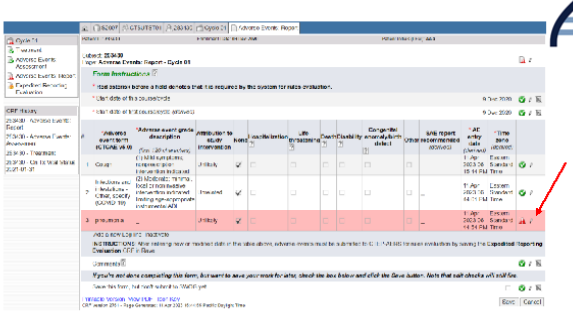

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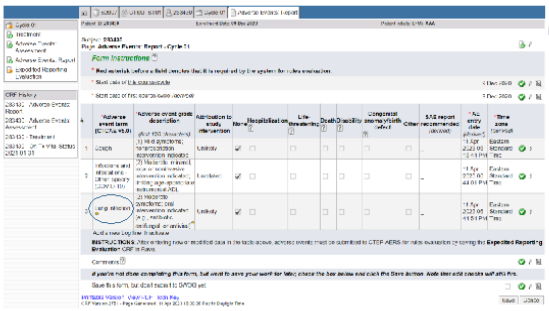

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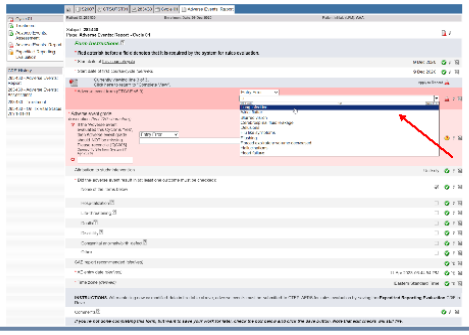

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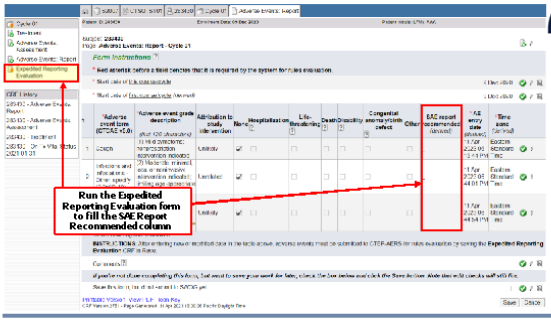

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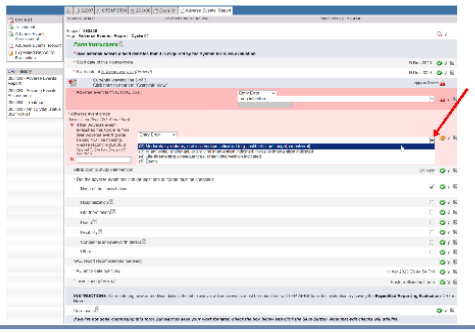
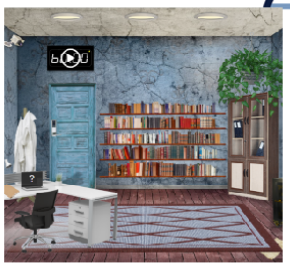


Adverse Event Escape Room Assessment

Designed to cover the various aspects of adverse event in a fun, interactive learning environment.

- You are locked in a room and need to solve various clues related to adverse events.
- Each clue leads to a number in the code to escape the room.
- Resources are available on the bookshelf in the room.
- Use the QR code to access
- Click on the question mark to start.



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- Also refer to the ***CRA Manual (for Oncology Research Professionals)***, available on the CRA Workbench!