Adverse Event Reporting

SWOG Clinical Trials

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Adverse Event Reporting

- Definitions and Background
- Relevant Information in SWOG Protocols
- Reporting Adverse Events
  - Common Terminology Criteria for Adverse Events (CTCAE) Terms
  - Grades
  - Attribution
  - Status
- Online Data Submission: Adverse Events

Definitions and Background

Adverse Event (AE):

Any change in the patient's condition from the day protocol treatment began, regardless of cause.

Examples:

- Nausea and/or vomiting caused by treatment
- Sinusitis from seasonal allergies
- Breaking a leg
- Increasing cancer symptoms

Toxicity:

Adverse symptom(s) caused or possibly caused by the drugs or treatment used in the study.

Tissue	Toxicity
Bone marrow	Myelosuppression
Mucous membranes	Nausea/Vomiting
Hair follicles	Alopecia

Serious Adverse Event (SAE):

An unexpected or severe reaction to protocol treatment.

Adverse Event Reporting

Expedited reporting: Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

Routine reporting: All adverse events, regardless of attribution or grade (unless otherwise specified in forms or protocol)

Why do we collect routine AEs?

- **Phase I trials:**
  - Primary objective: to assess the safety of an experimental regimen and determine the maximum tolerated dose
- **Phase II single-arm trials:**
  - Secondary objective: to estimate the frequency and severity of toxicities in trial regimen
- **Phase II/III randomized trials:**
  - Secondary objective: to compare the frequency and severity of toxicities associated with each regimen

Information in SWOG Protocols

Protocol Table of Contents

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

…and the Master Forms Set!

Protocol Section 3: Drug Information

- Lists known human toxicities for each study drug

Protocol Section 8:

Toxicities to be Monitored and Dose Modifications

- Lists certain toxicities that may be seen on treatment
- Details dosage changes required during treatment in response to AEs

Protocol Section 8:
Toxicities to be Monitored and 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

Protocol Section 8:
Toxicities to be Monitored and Dose Modifications

- Lists drugs to aid in symptom management
- Lists names and contact information of physicians to reach for assistance
- Identifies version of Common Terminology Criteria for Adverse Events (CTCAE) used for study reporting

Protocol Section 9:
Study Calendar

- Indicates how often to assess adverse events while receiving protocol treatment

Protocol Section 16: Ethical and Regulatory Considerations

- Includes instructions for reporting SAEs and AESIs (if applicable)

Master Forms Sets/All Forms Packet

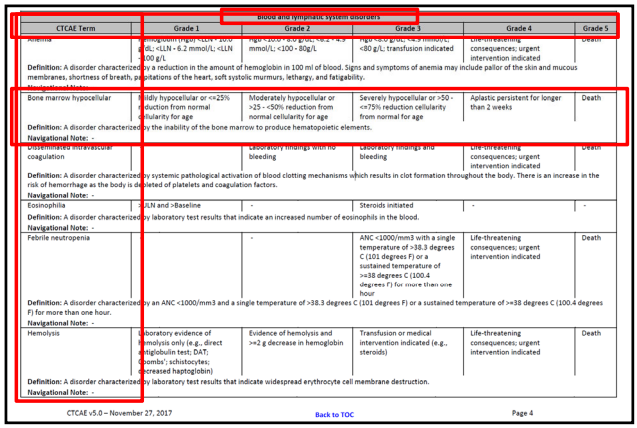
- Contains all study forms, including those used to document adverse events

Reporting Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE)

Common Terminology Criteria for Adverse Events (CTCAE)

- Provides a list of specific adverse events ("CTCAE terms"), a description of each adverse event term, and guidelines on how to grade each event.
- Can find a copy of the CTCAE at <ctep.cancer.gov>
  - Version 4.0: In use since October 2009
  - Version 5.0: Published in November 2017
    - All SAE reporting starting April 1, 2018
    - Routine AE reporting on all new studies
- Some studies may use a different CTCAE version for routine AE reporting vs. SAE reporting



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: -					

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CTCAE Terms

- The terms might not always be listed the way you expect. Below are some examples of common AEs and the appropriate CTCAE v 5.0 term:

Pneumonia	***Lung infection***
Thrombocytopenia	***Platelet count decreased***
Shortness of breath	***Dyspnea***

- Each system category also includes an "Other" option (for example, "Investigations – Other"), but only use as a last resort.

CTCAE Grades

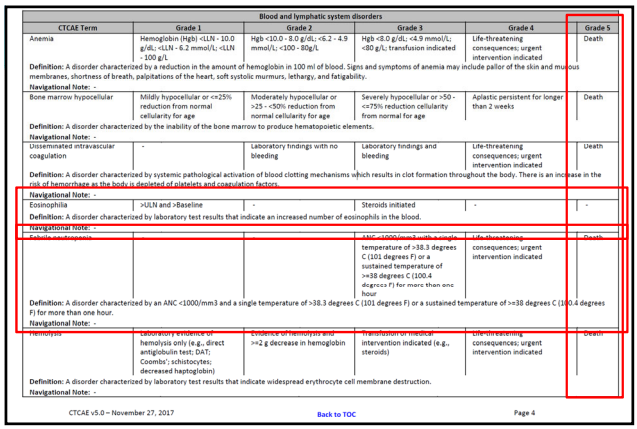
Grade 1 Mild

Grade 2 Moderate

Grade 3 Severe or medically significant but not immediately life-threatening

Grade 4 Life-threatening consequences

Grade 5 Death related to AE



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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 Investigational 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 Investigational 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

Status

The status code describes the state of the adverse event at various points throughout the study:

- New
- Continues at the same or lower grade
- Increased grade OR improved then worsened

Additional AE Data Collection Items

Some additional data items that may be collected for each AE include:

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

General Rules for AE Reporting

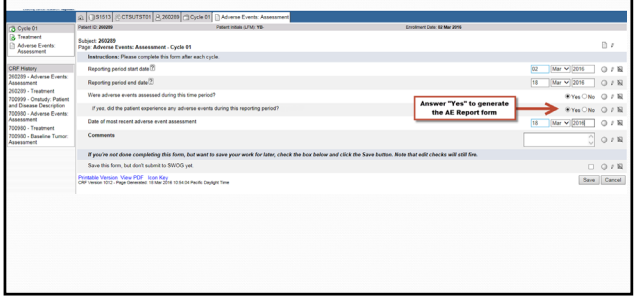
- Record and report adverse events as they occur
- List all adverse events, regardless of clinical significance
  - Exception: Only report AEs present at baseline if they worsen or reoccur after previously resolving
- On each cycle or reporting period: record the most severe grade experienced
- Avoid using "Other" CTCAE terms unless no specific CTCAE term applies
- When in doubt, document it!

Online Data Submission: Adverse Events

- CRA Workbench (legacy trials only)
- **Medidata Rave**
  - AE data submission
  - New NCI-mandated AE form with CTEP-AERS integration

Online AE Submission
Medidata Rave

Online AE Submission: Medidata Rave



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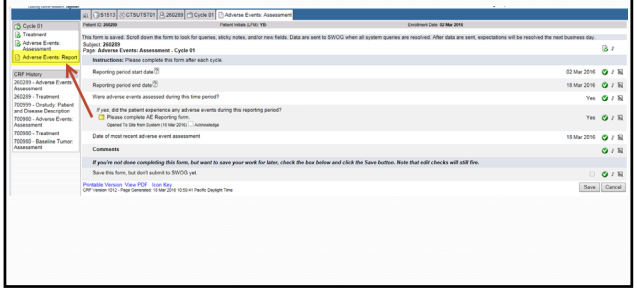

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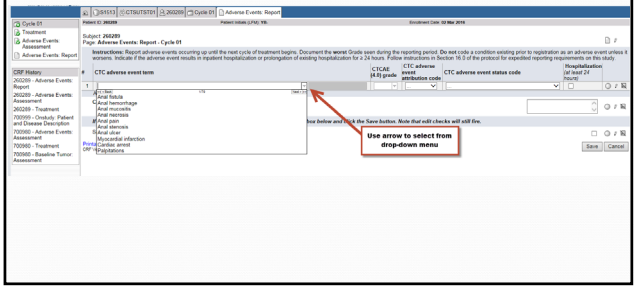

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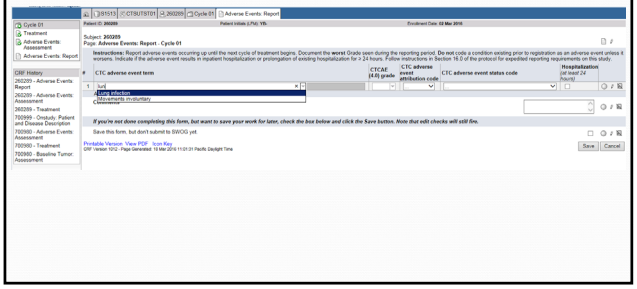

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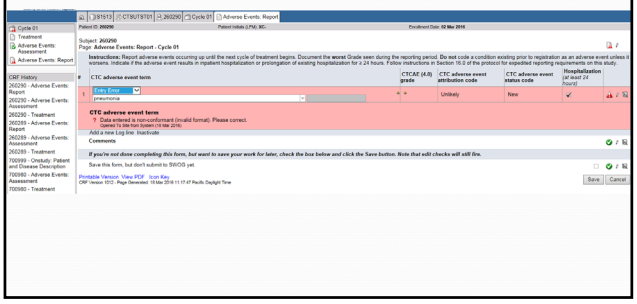

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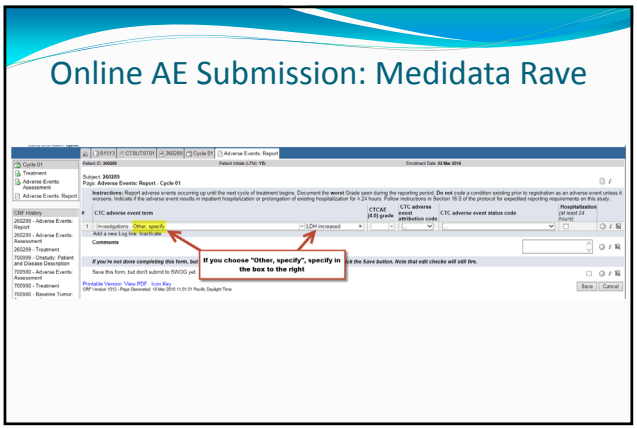

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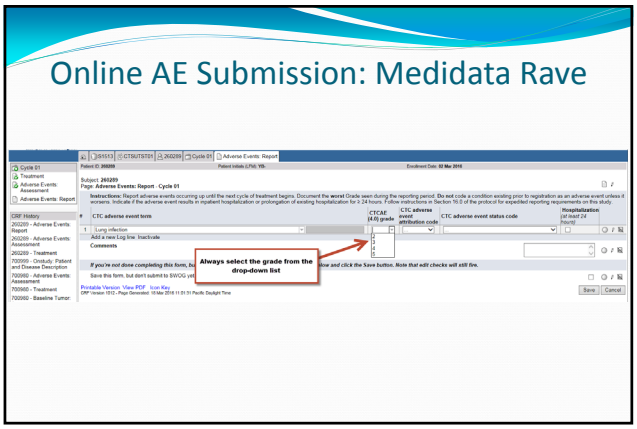

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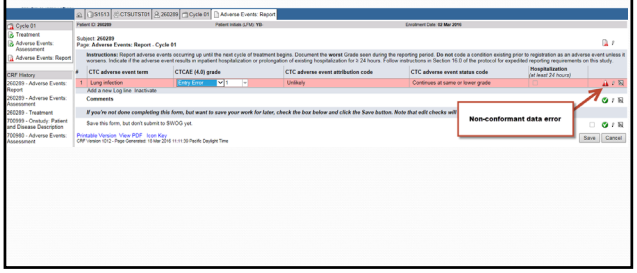

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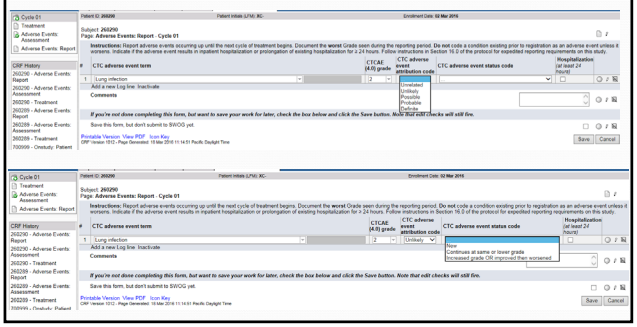

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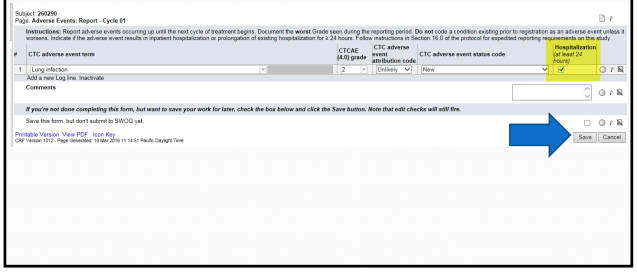

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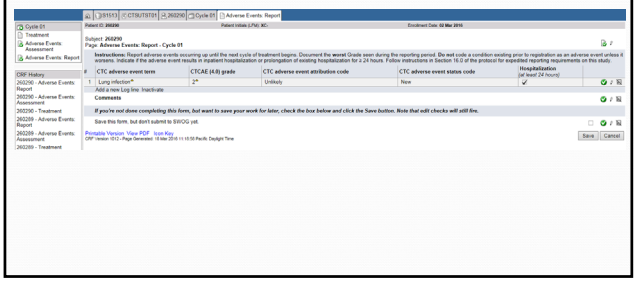

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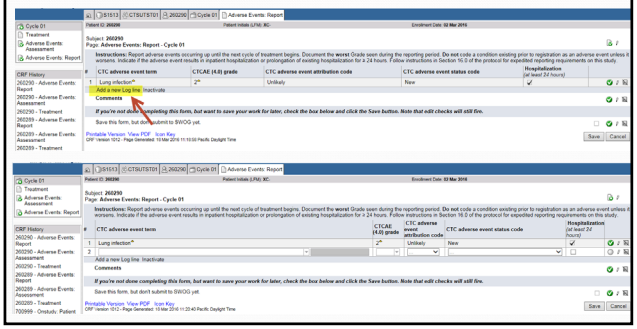

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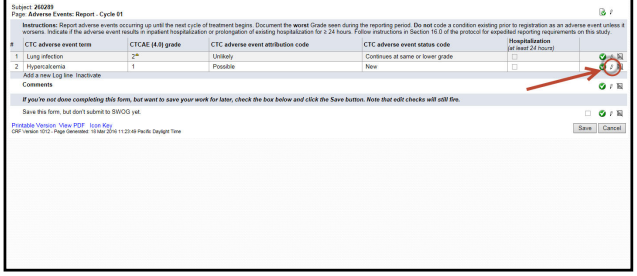

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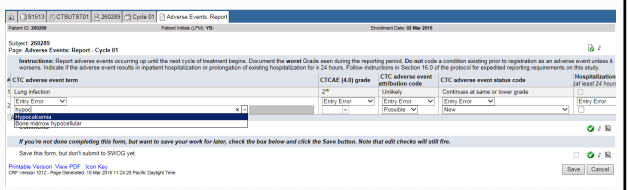
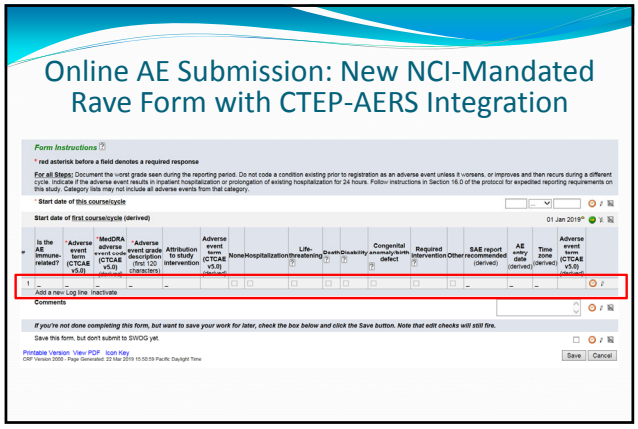


Online AE Submission
New NCI-Mandated Rave Form with CTEP-AERS Integration

Online AE Submission: New NCI-Mandated Rave Form with CTEP-AERS Integration

- CTSU has created Rave Adverse Events forms that integrate directly with the CTEP-AERS expedited reporting system
  - Reduces double data entry
- All new SWOG studies are required to use this form to collect adverse events
  - S1505 was the pilot SWOG study to use this form
  - Currently, ten active trials across most disease sites
  - Five studies currently in development
- For studies using this form, SAEs must be entered in Rave first

Online AE Submission: New NCI-Mandated Rave Form with CTEP-AERS Integration



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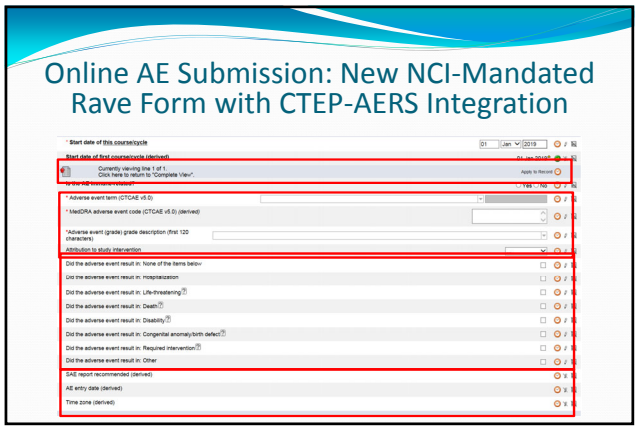

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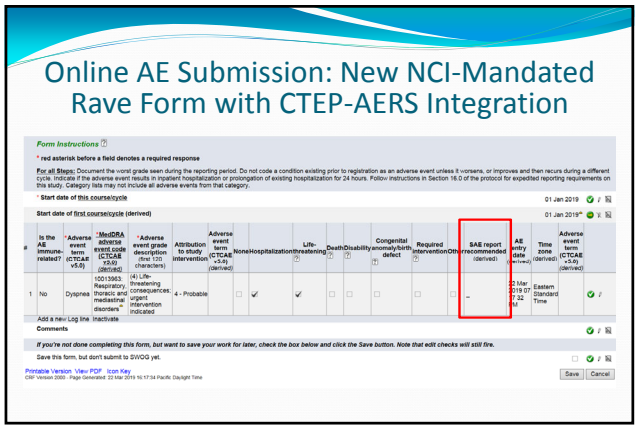

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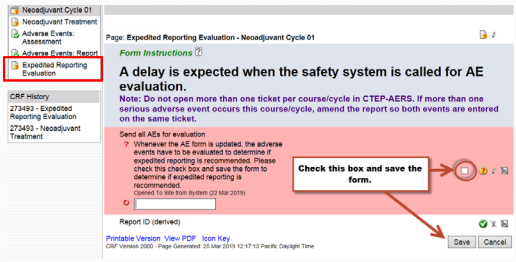

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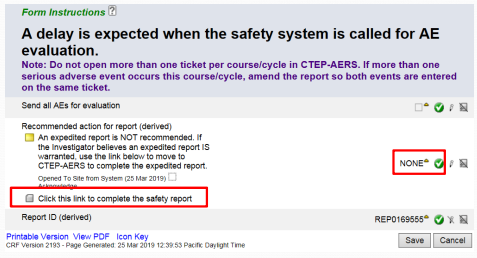

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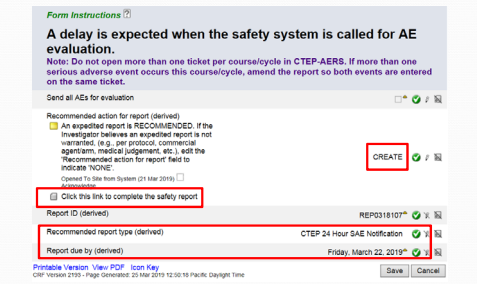

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LungMAPQuestion@crab.org
LymphomaQuestion@crab.org
MelanomaQuestion@crab.org
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And refer to the ORP Manual available at
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