Adverse Event Assessment & Reporting

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SWOG CANCER RESEARCH NETWORK
NCI National Clinical Trials Network
a National Cancer Institute program
NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

What is your current role?

A. Data Management
B. Clinical Research Nurse
C. Regulatory Affairs
D. Quality Assurance
E. Administration
F. Other

What is the definition of an Adverse Event?

A. A known toxicity of the study agent.

B. Any untoward sign or symptom that occurs during the course of a clinical trial.

C. Any event which the PI decides to report during the course of a clinical trial.

D. A side effect caused by the study agent.

ADVERSE EVENT (AE)

U.S. Office for Human Research Protections (OHRP)	U.S. Food and Drug Administration (FDA)	International Council on Harmonization (ICH)
Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

SWOG Definition

Any unfavorable and unintended change in a patient's condition from the day protocol treatment began, REGARDLESS OF EXPECTEDNESS OR RELATIONSHIP TO RESEARCH.

https://txwb.crab.org/TXWB/CRA_MANUAL/Vol1/chapter%2015_Adverse%20Event%20Assessments.pdf

Unexpected Event

U.S. OHRP	U.S. FDA	ICH
Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either: • the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; **OR** • the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.[2]	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

Data Standards for AE Terms

Medical Dictionary for Regulatory Activities (MedDRA)

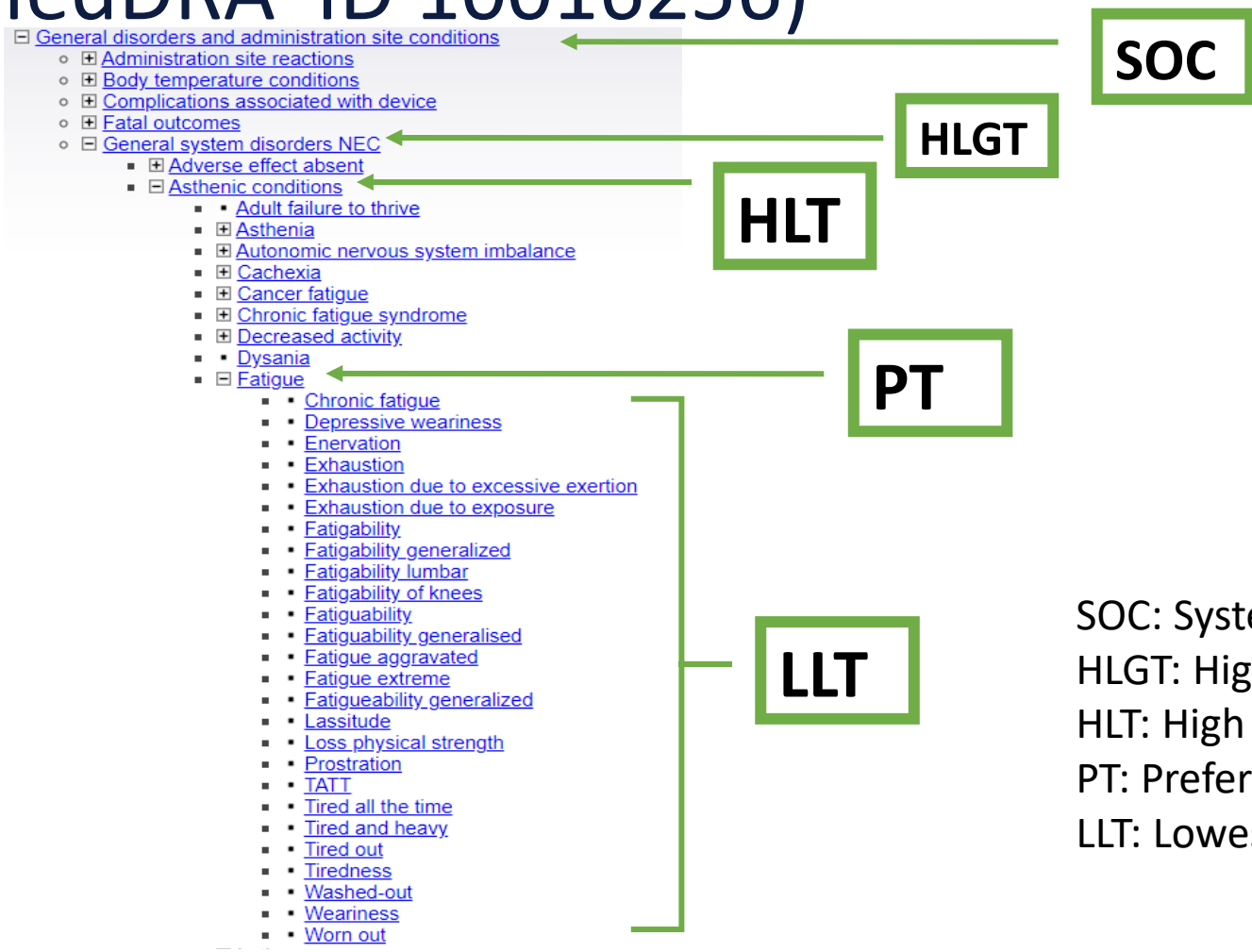
Common Terminology Criteria for Adverse Events (CTCAE)

Medical Dictionary for Regulatory Activities (MedDRA)

- Dictionary of clinically validated international medical terminology
- Developed by the International Council on Harmonisation (ICH)
- Used to facilitate sharing of regulatory information internationally for human medical products
- Available in 19 languages
- http://www.meddramsso.com/

MedDRA

MedDRA v. 25.0 'Fatigue' hierarchy displayed (MedDRA ID 10016256)



KEY

SOC: System Organ Class
HLGT: High Level Group Term
HLT: High Level Term
PT: Preferred Term
LLT: Lowest Level Term

Common Terminology Criteria for Adverse Events (CTCAE)

- Developed by NCI Cancer Therapy Evaluation Program (CTEP) as the Common Toxicity Criteria (CTC) in 1983
- Fundamentally agreed upon terminology for AEs that occur in oncology research
- Current version: 5
- Early 2024: version 6
- Organized by MedDRA
  - SOC (minus Product Issue SOC)
  - LLT

CTCAE v 5

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					

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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!

Severity Rating or Grading

Measures the severity of clinical findings and impact on the participant.

Promotes consistency for severity assessment.

Facilitates common understanding of shared AE data sets.

Provides framework to compare AEs across different studies.

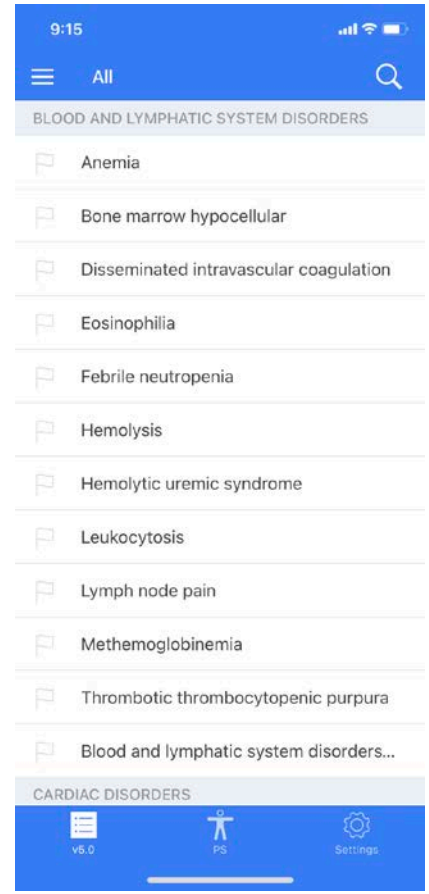
Reporting Adverse Events: CTCAE Grade

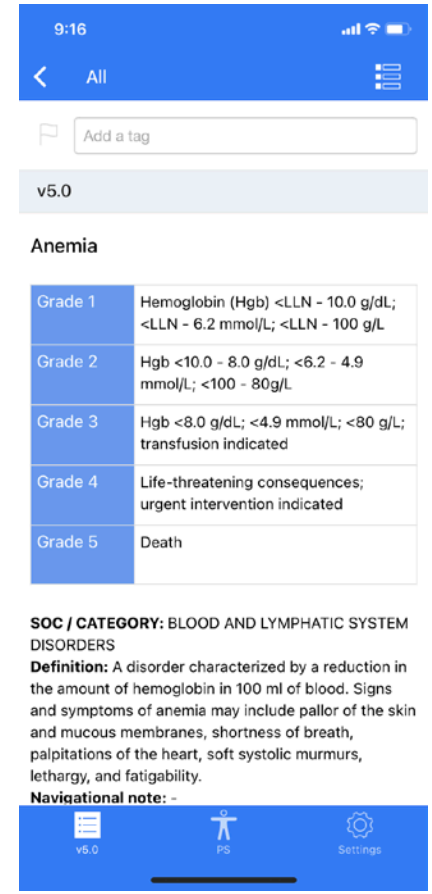
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; < LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L; transfusion indicated	Life-threatening consequences; urgent intervention 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.					

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

How to Access CTCAE

- Smartphone & tablet apps available
  - Use CTCAE+
  - Easy search feature
- NCI website
  - Search pdf version





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

Determining Attribution…

What is already known about:

- Drug or classification of the drug
- Therapy or intervention
- Expectedness

Is there a temporal relationship of the AE to the study intervention?

Does the AE improve or disappear when the intervention is discontinued?

If re-challenged with the intervention, does the AE reappear?

- At the same severity?
- At the same time point?

… Determining Attribution

Is the AE a result of existing disease signs and symptoms?

Is the AE a result of existing baseline signs and symptoms?

Is the AE a result of an underlying concurrent medical condition(s)?

Is the AE a result of an underlying concurrent medication(s)?

AE Assessment

- Obtained by nurse or investigator with input from the other members of the research team.
- Starts with a quality baseline assessment.
- Includes:
  - Physical exam
  - Review of medical record
  - Review of Laboratory Tests
  - Review of Radiology results
  - Review of Signs & Symptoms
- Solicited events vs spontaneously reported by a participant

Documentation

- Medical Record documentation should include:
  - Date the event began; include time with infusion reaction.
  - Detailed description
  - Attribution
  - Immune relationship if applicable
  - Any treatment for the event
  - Impact on the clinical trial intervention
  - Date of resolution/improvement
  - Seriousness

Example of documentation

Patient Name:____________________ Study # ____________________ Cycle: _______________

AE	Grade	Attribution	Start	Stop	Ongoing	Immune Related	Is this considered a serious AE needing expedited reporting	Action taken
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	
					☐	☐ Yes ☐ No	☐ Yes ☐ No	

Attribution: 1 definitely related; 2 unlikely related; 3 possibly related; 4 probably related; 5 unrelated

Investigators Signature: ______________________ Date: ________________________ Page: _____ of _____

Which statement represents the most complete description for adverse event reporting?

A. Ms. Smith states she had some diarrhea after her last treatment, that stopped with Imodium.

B. She stated she had 6 stools a day after her last treatment. The diarrhea stopped 4 days ago.

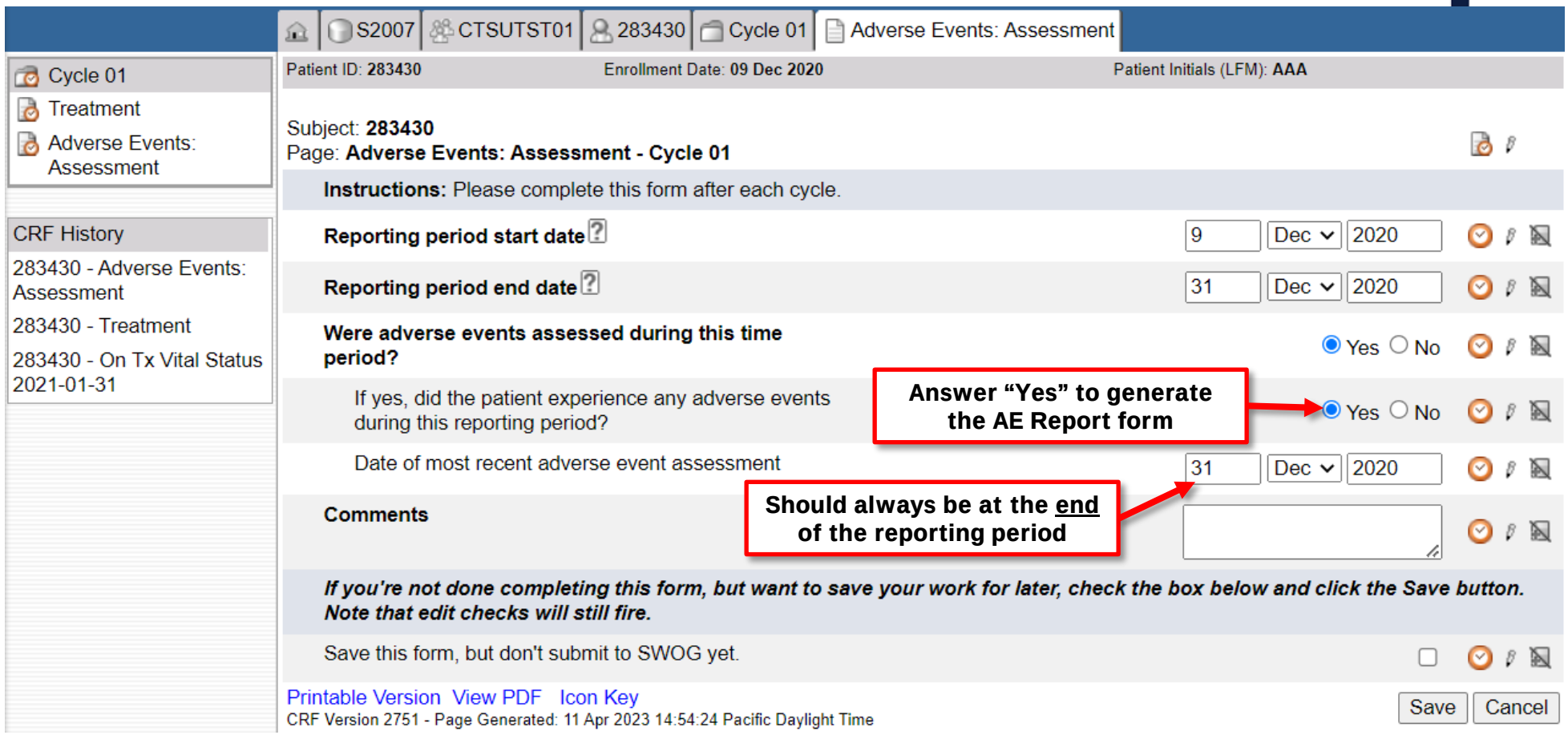
C. Patient states she had 6 stools a day, which is 5 above baseline.

D. She states she had 6 stools a day, which is 5 above baseline. This started 5 days after her treatment. She took Imodium, and it slowed to 2 stools a day yesterday.

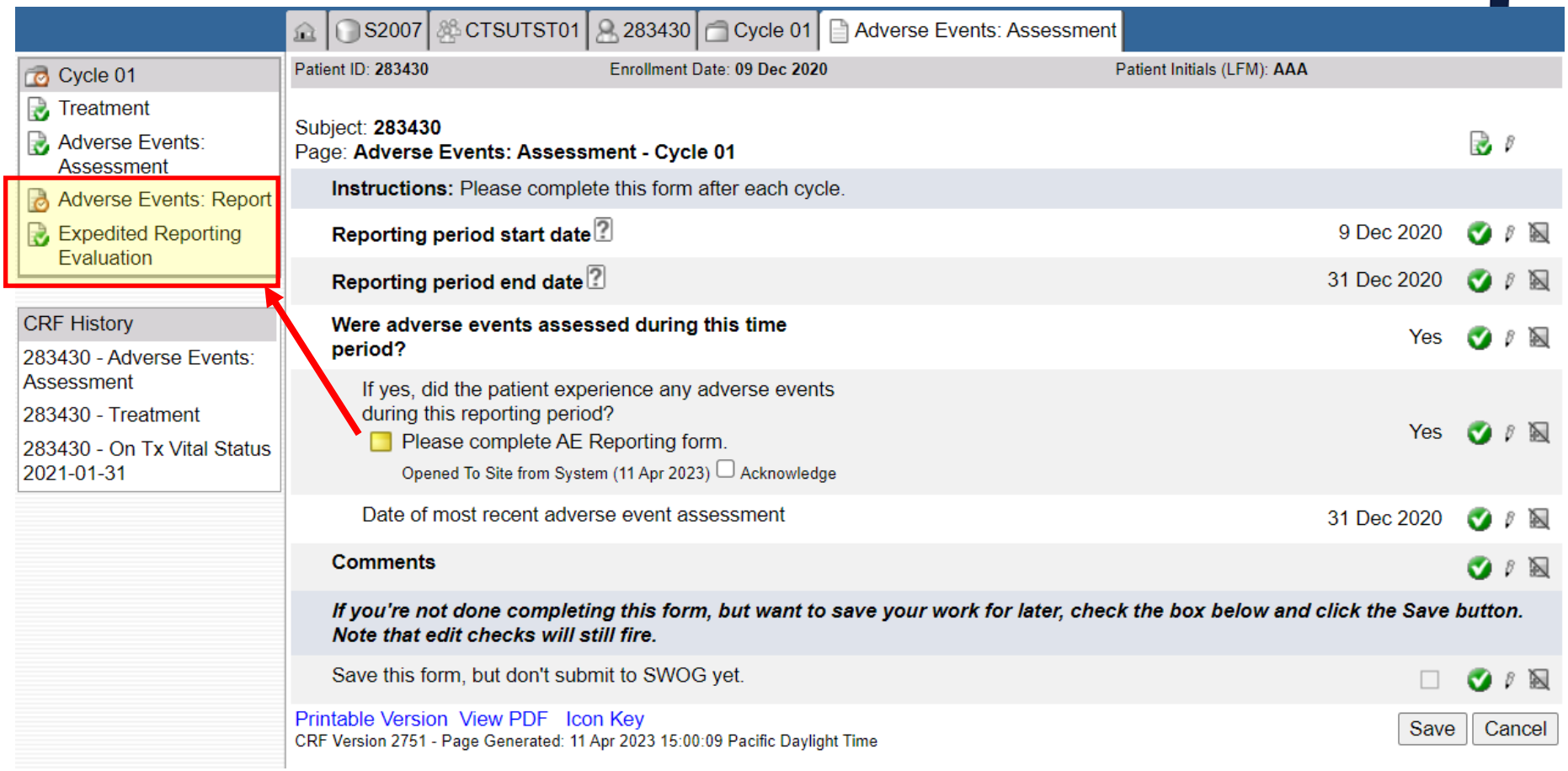
Online Data Submission

Adverse Events

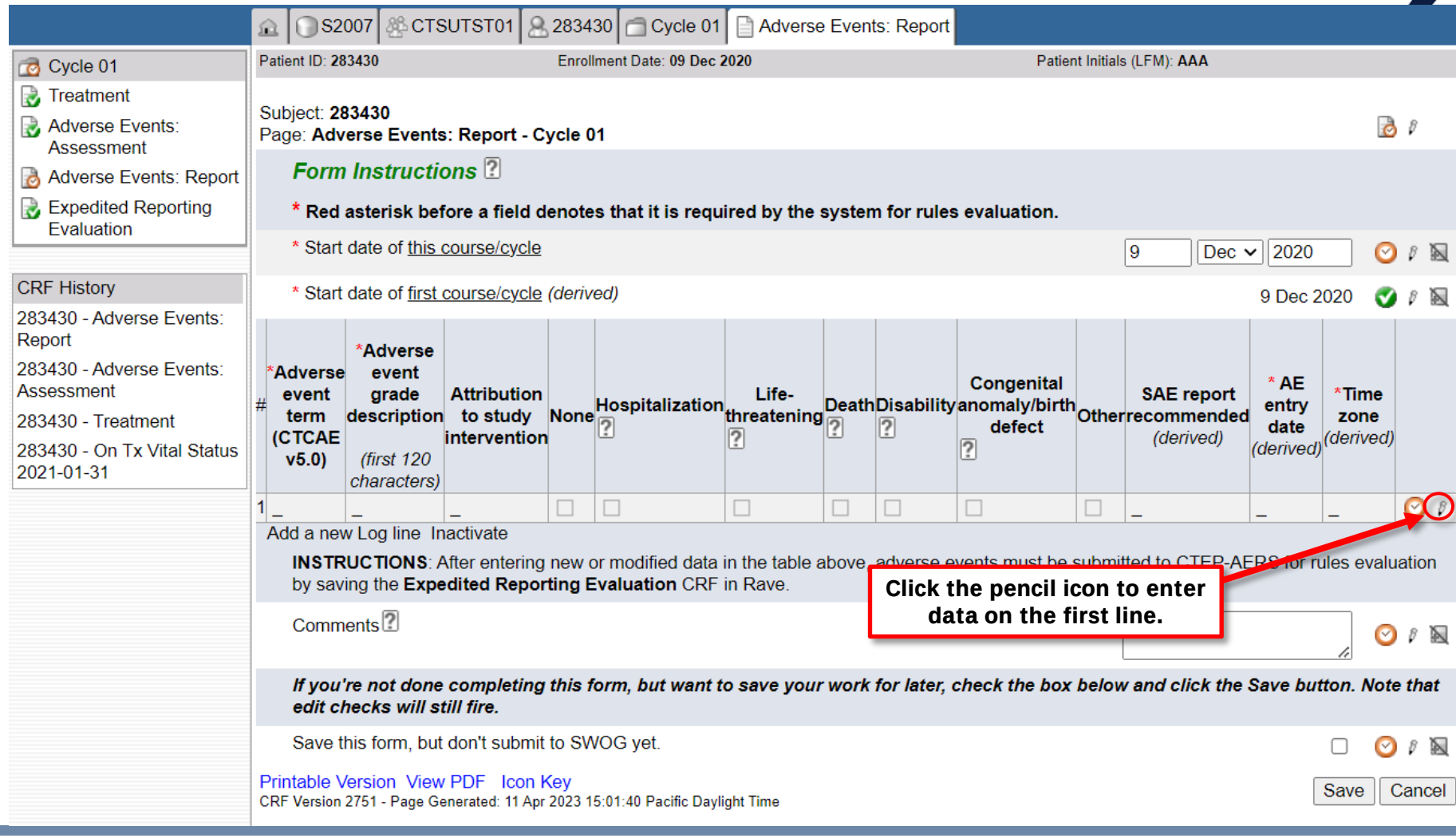
Online Data Submission: Adverse Events



Online Data Submission: Adverse Events



Online Data Submission: Adverse Events



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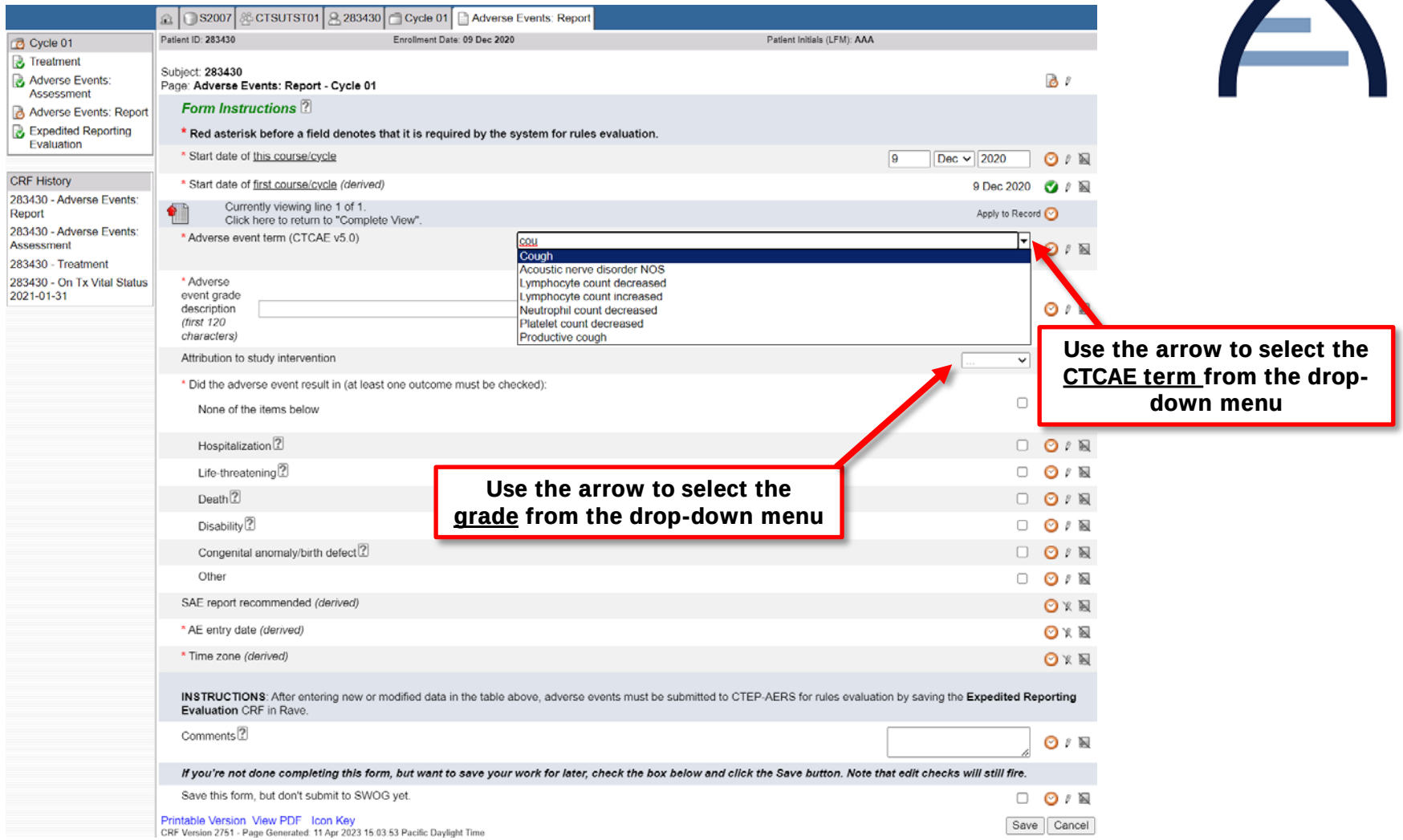
Online Data Submission: Adverse Events



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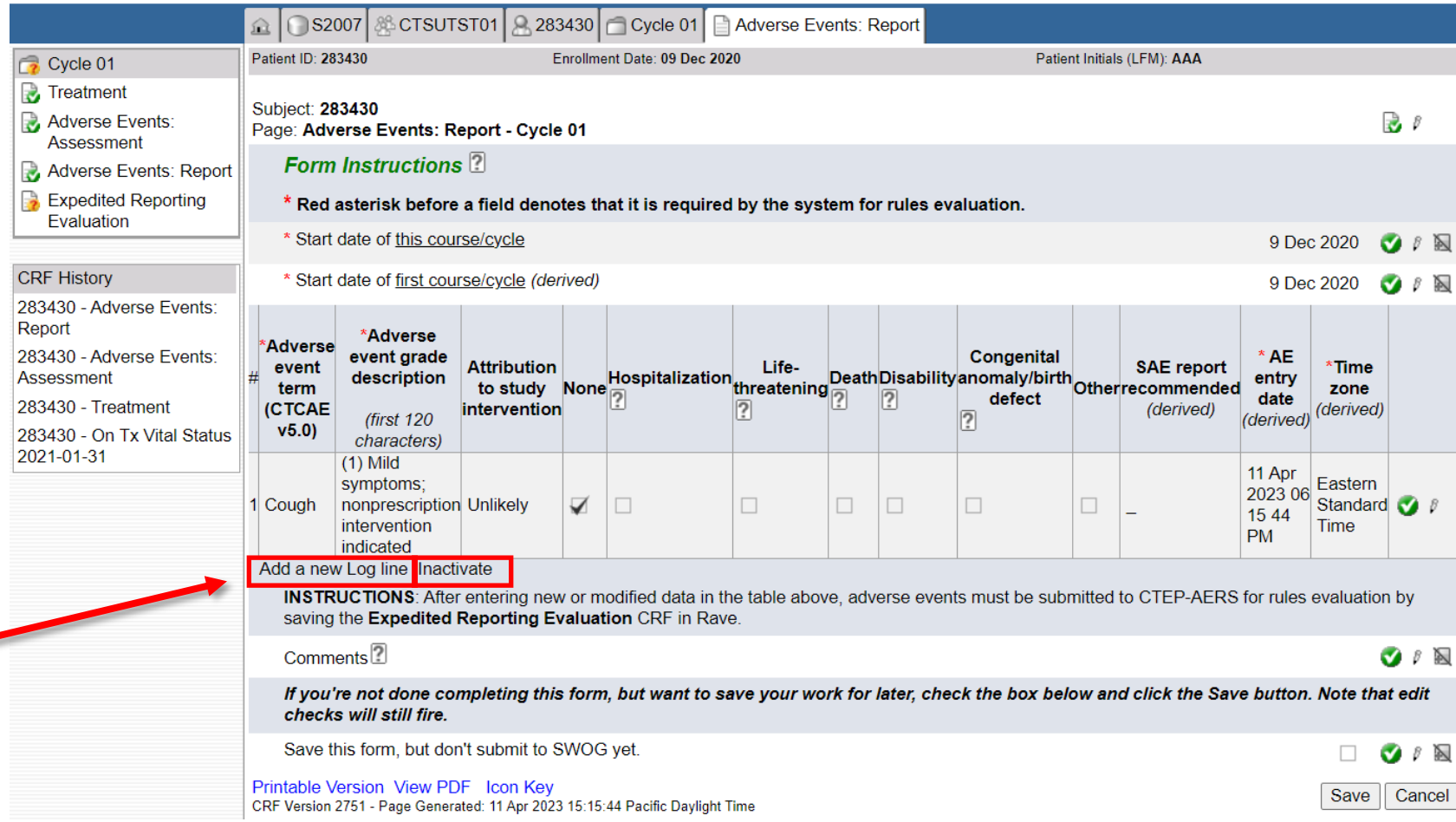
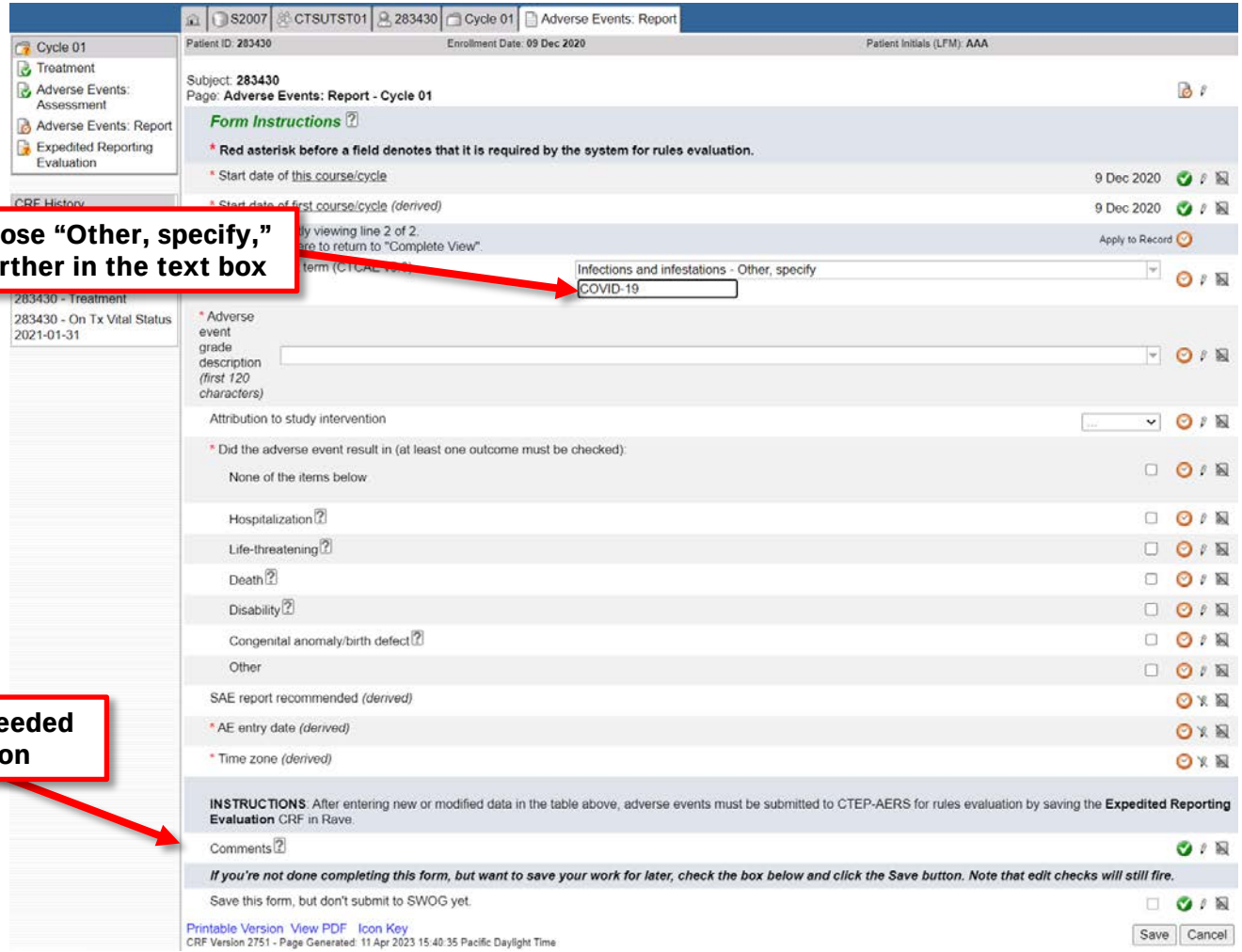


(2018) CTEP Guidance for recording adverse event start & end dates

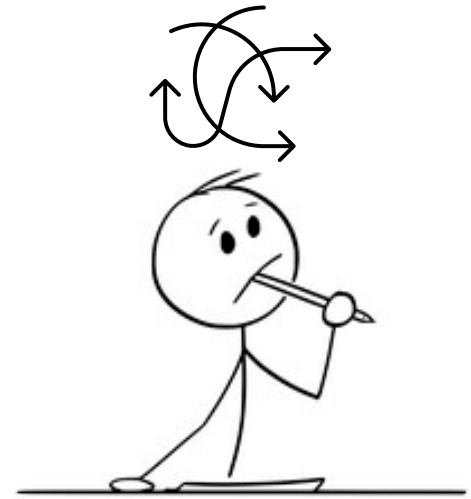
Online Data Submission: COVID-19



If you choose "Other, specify," specify further in the text box

Use the Comments as needed for further explanation

Nuances in AE Reporting



Common Reporting Errors

- Non-clinically significant lab abnormalities
- Symptoms vs Condition
- Procedure vs disease that resulted in the procedure
- Progression
- Not reporting baseline conditions that worsen or reoccur after previously resolving.

Grading based on the use of Medication

Just because someone is taking a medication, does not mean that they have the condition.

- Prophylactic use
- Medications have multiple uses

Grading conditions present at Baseline

Not all events can be assigned a grade at baseline.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypertension	**Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; **Pediatric:** Systolic/diastolic BP >90th percentile but< 95th percentile; **Adolescent:** BP ≥120/80 even if < 95th percentile	**Adult:** Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated;	**Adult:** Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; **Pediatric and adolescent:** Systolic and/or diastolic > 5 mmHg above the 99th	**Adult and Pediatric:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

Which Cycle does an AE get reported in?

Screening	Registration	Cycle 1	Cycle 2
4/8/22	4/24/22 / NOON	4/27/22 / NOON Tx	5/25/22 / Noon Tx
☐ Dyspnea grade 2	☐ Labs at 9:00 am	☐ Labs drawn at 9:00 am	☐ Labs drawn at 9:00 am
☐ Anemia grade 2	☐ Physical at 9:30 am	☐ Physical at 9:30 am	☐ Physical at 9:30 am

Adverse events	Adverse events	Adverse Events
Anemia gr 1	Anemia gr 0	Anemia gr 1
Dyspnea gr 3	Dyspnea gr 2	Dyspnea gr 1
Albumin gr 1	Albumin gr 1	Albumin gr 1
	Fatigue gr 1	Fatigue gr 2

Below are some events that occurred during Cycle 1. Which one(s) should be reported, based on general SWOG guidance on AE reporting:

1. Fatigue, gr 1, attributed to working long hours, was 0 at baseline.
2. Increased non-fasting glucose, previously WNL. Not clinically significant.
3. Shortness of breath gr 2, same as baseline.
4. 5% weight loss, found on Day 1 of Cycle 2, prior to treatment.

A. All listed events
B. Fatigue & Shortness of Breath
C. Fatigue, increased glucose & weight loss.
D. Fatigue, increased glucose & shortness of breath.

Adverse Event Escape Room

https://docs.google.com/presentation/d/1cm_dIq8VsnkjJd5R4vPUcXZ4s3UfYzMO002IWxD17RE/preview?slide=id.p

Questions