MERCK

Welcome to

Adverse Experience Reporting

e-Learning Module

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- **Review basic definitions**

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- **Why report adverse experiences?**

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Adverse Experience Reporting

e-Learning Module

- **Review basic definitions**
- **Why report adverse experiences?**
- **What constitutes an adverse experience?**

Clinical Research
≠
Clinical Practice

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Top Priority

= Safety and Health of Participants

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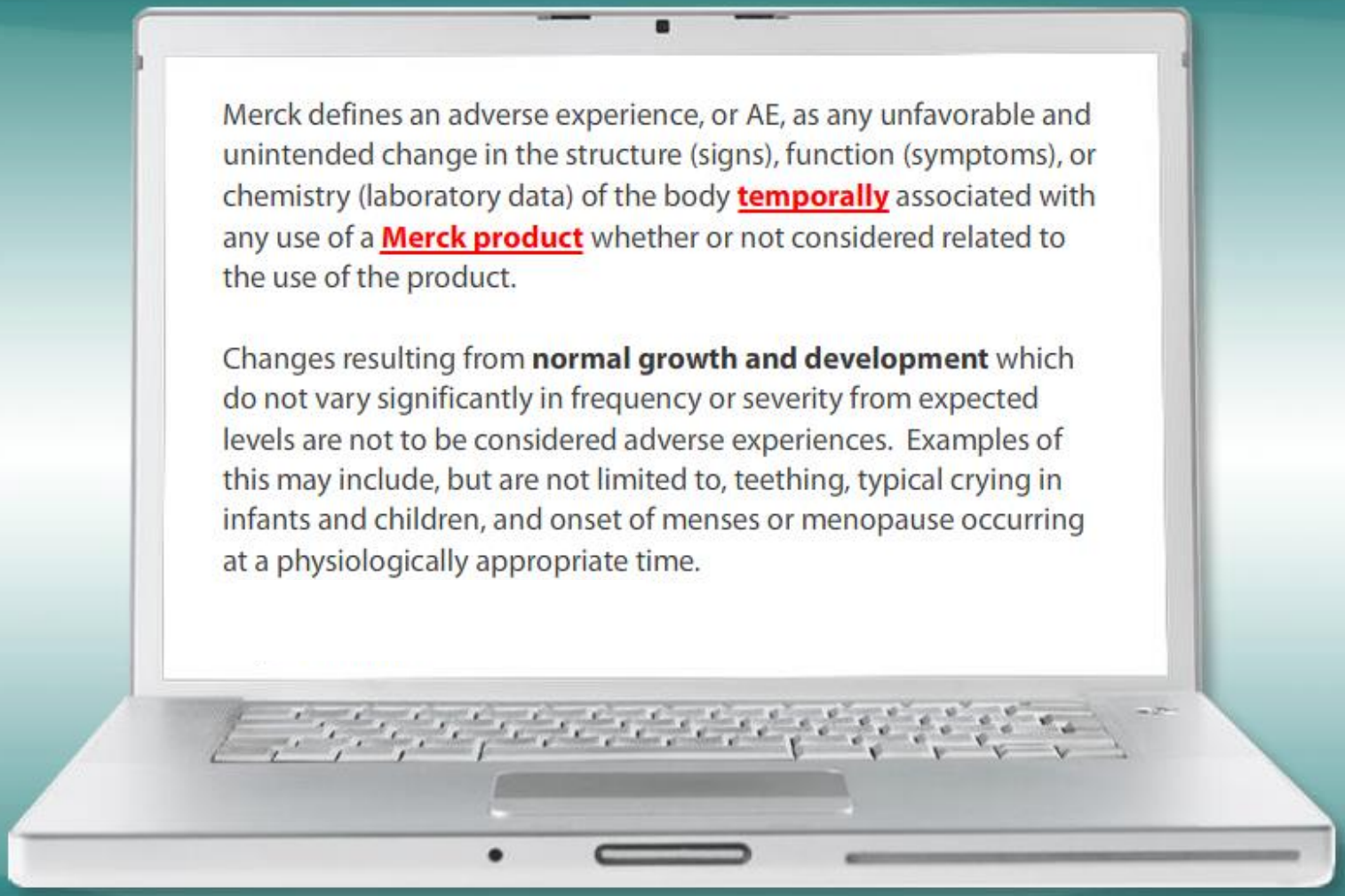
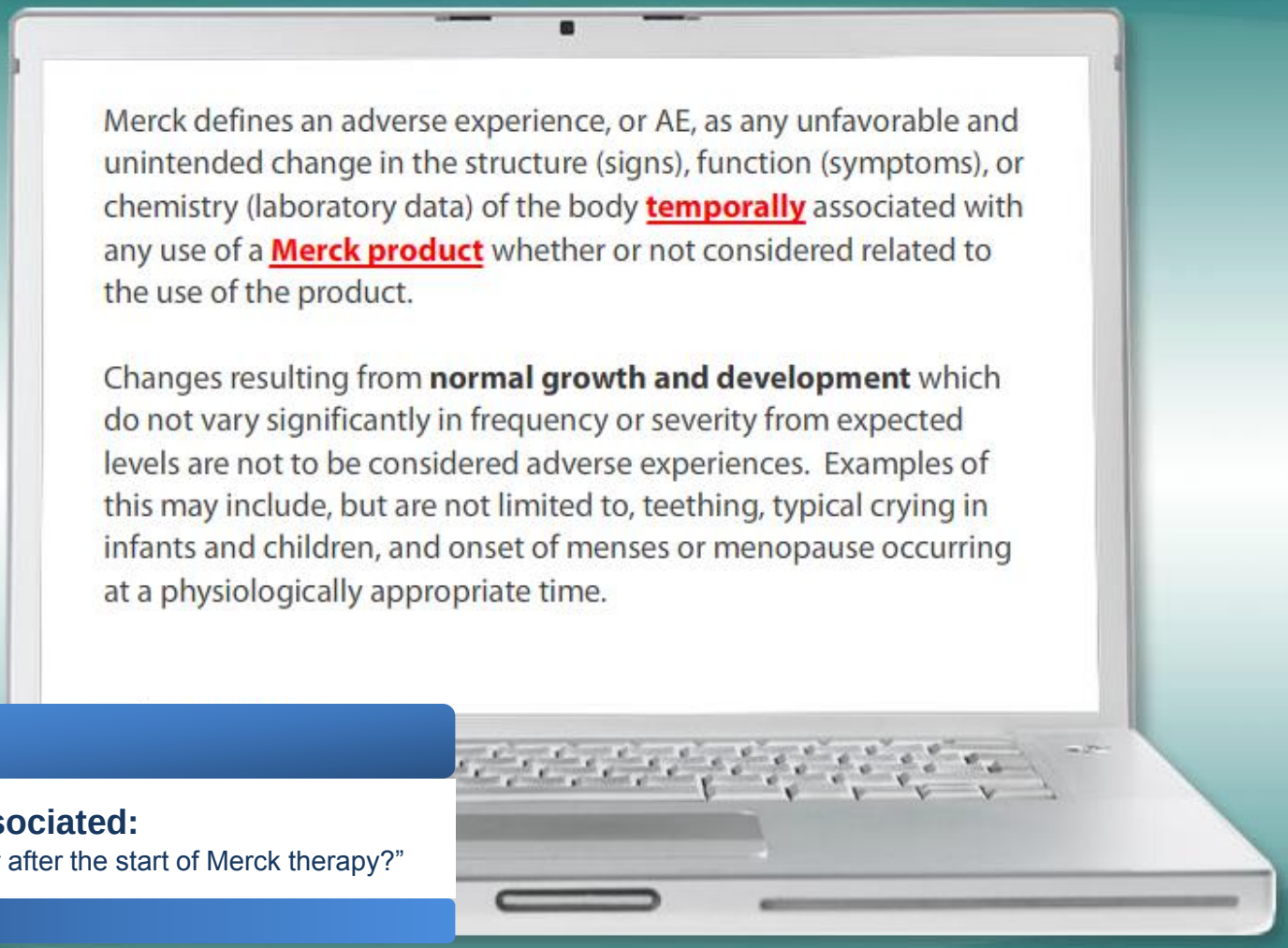
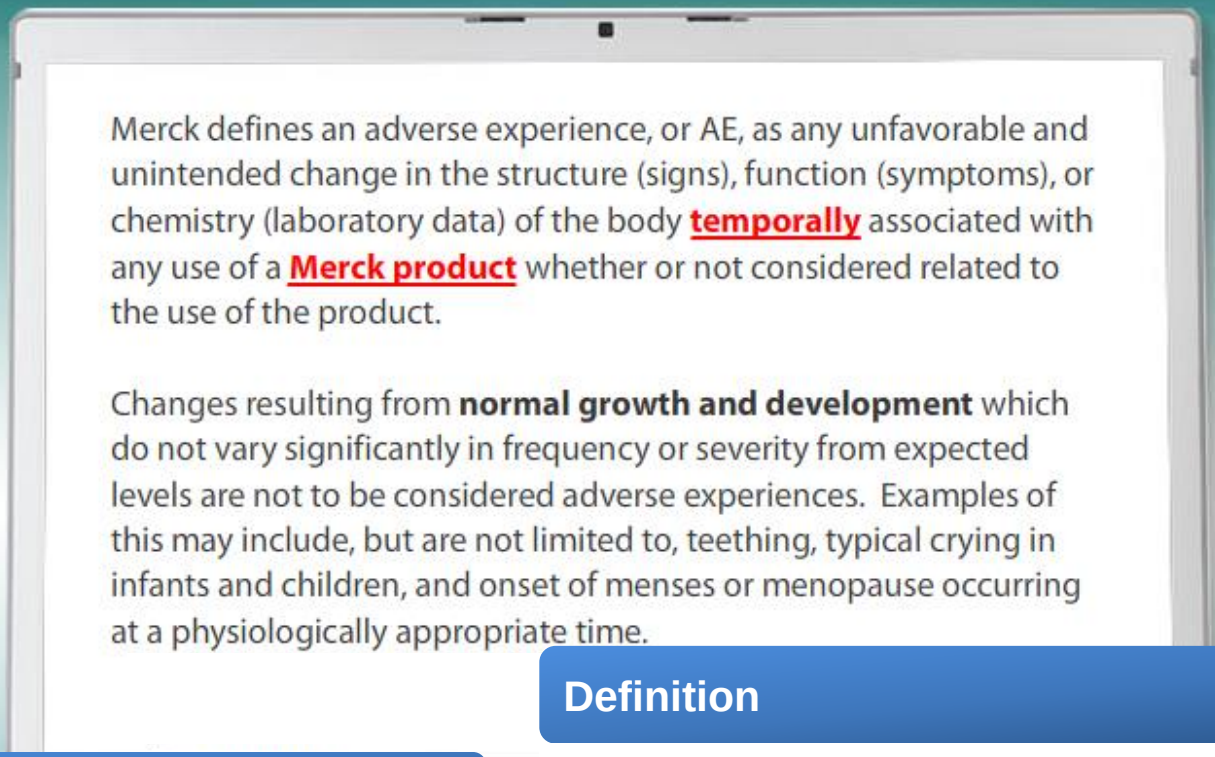




Explanation

Temporally associated:
"Did the event occur after the start of Merck therapy?"



Definition

Merck product:
"Any pharmaceutical product, biological product, device or diagnostic agent, whether investigational (including placebo or active comparator medication) or marketed by, manufactured by, licensed by, or distributed by Merck & Co., Inc. for human use."

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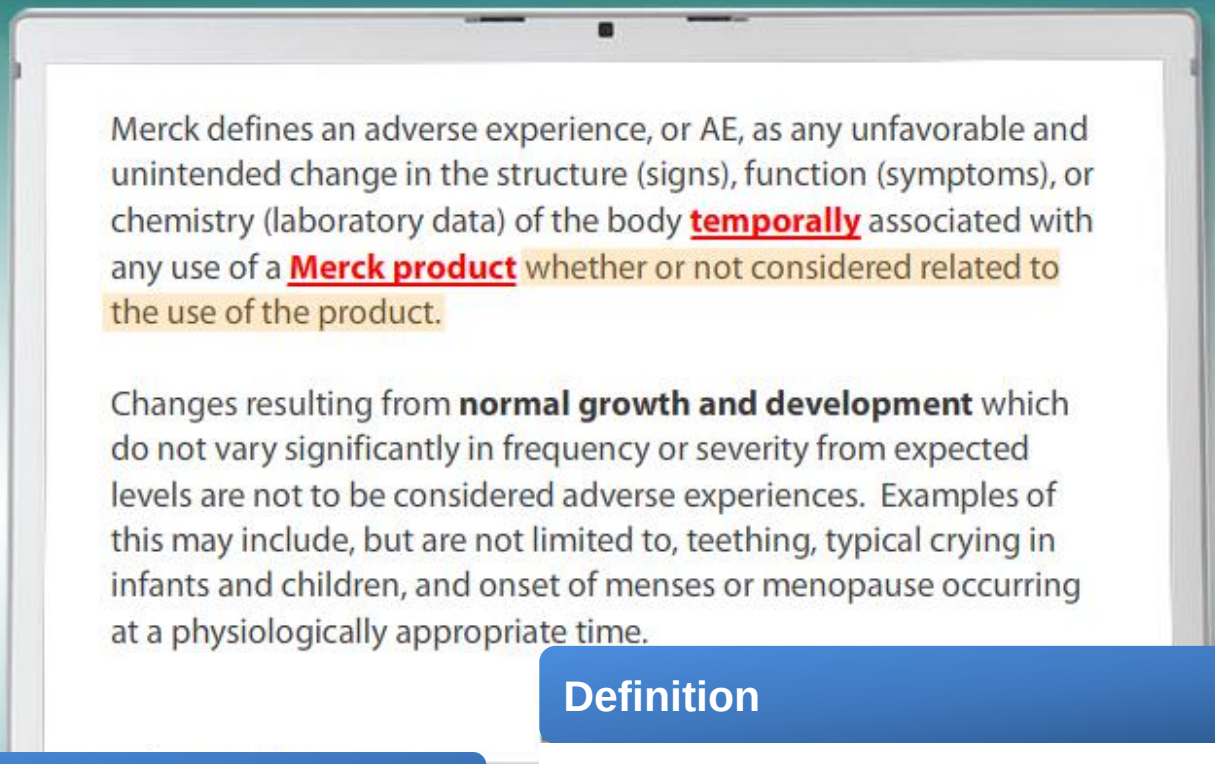

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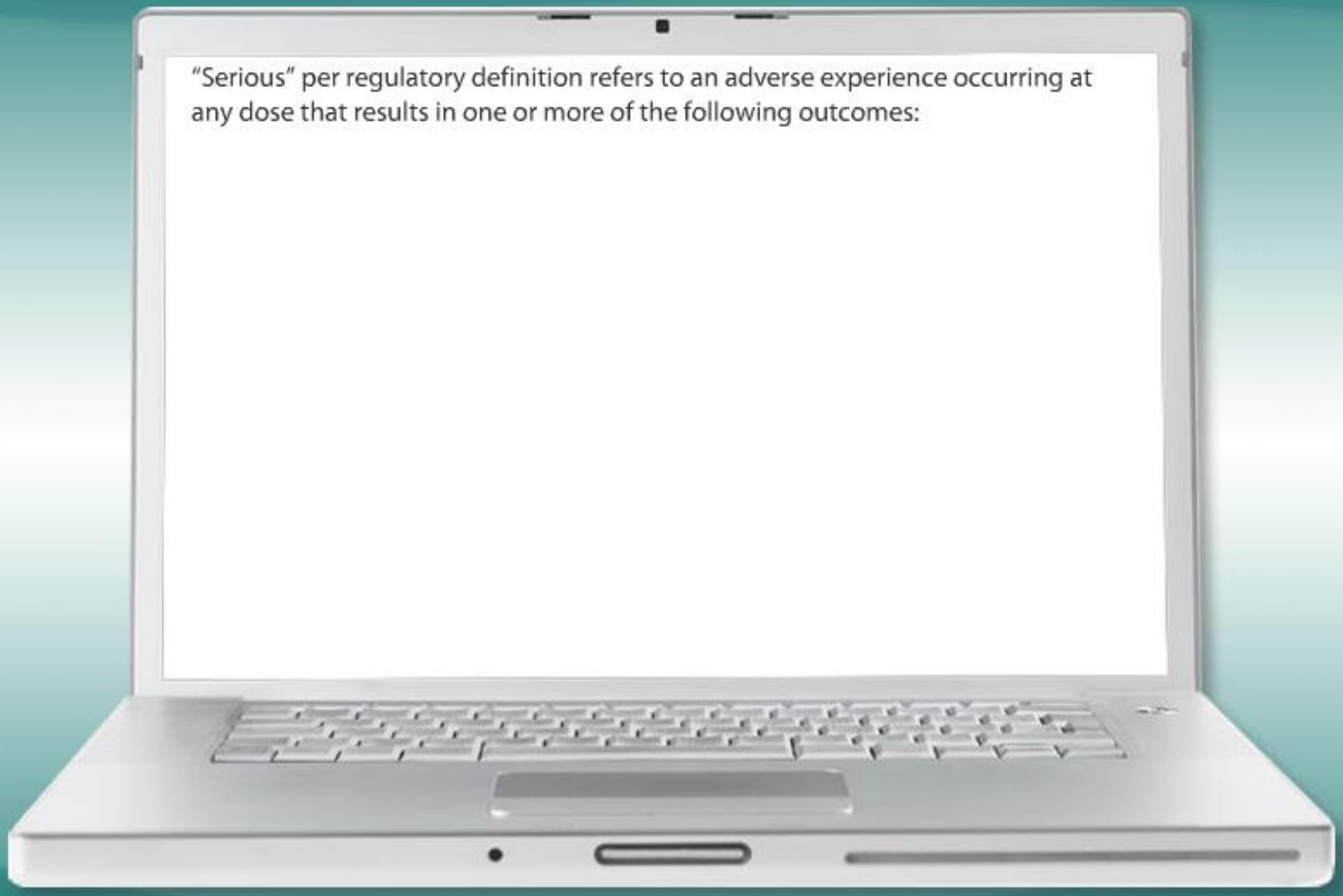

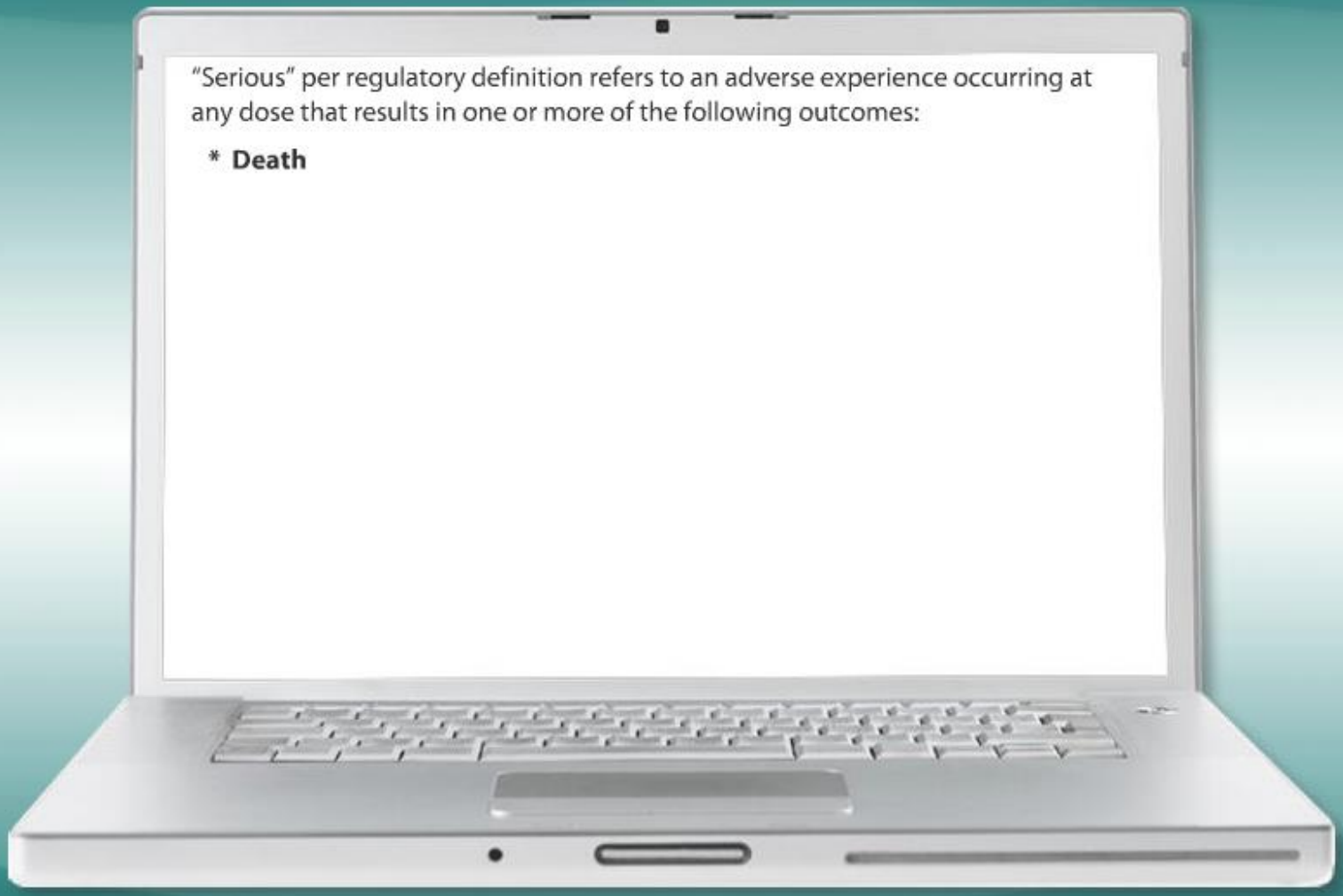

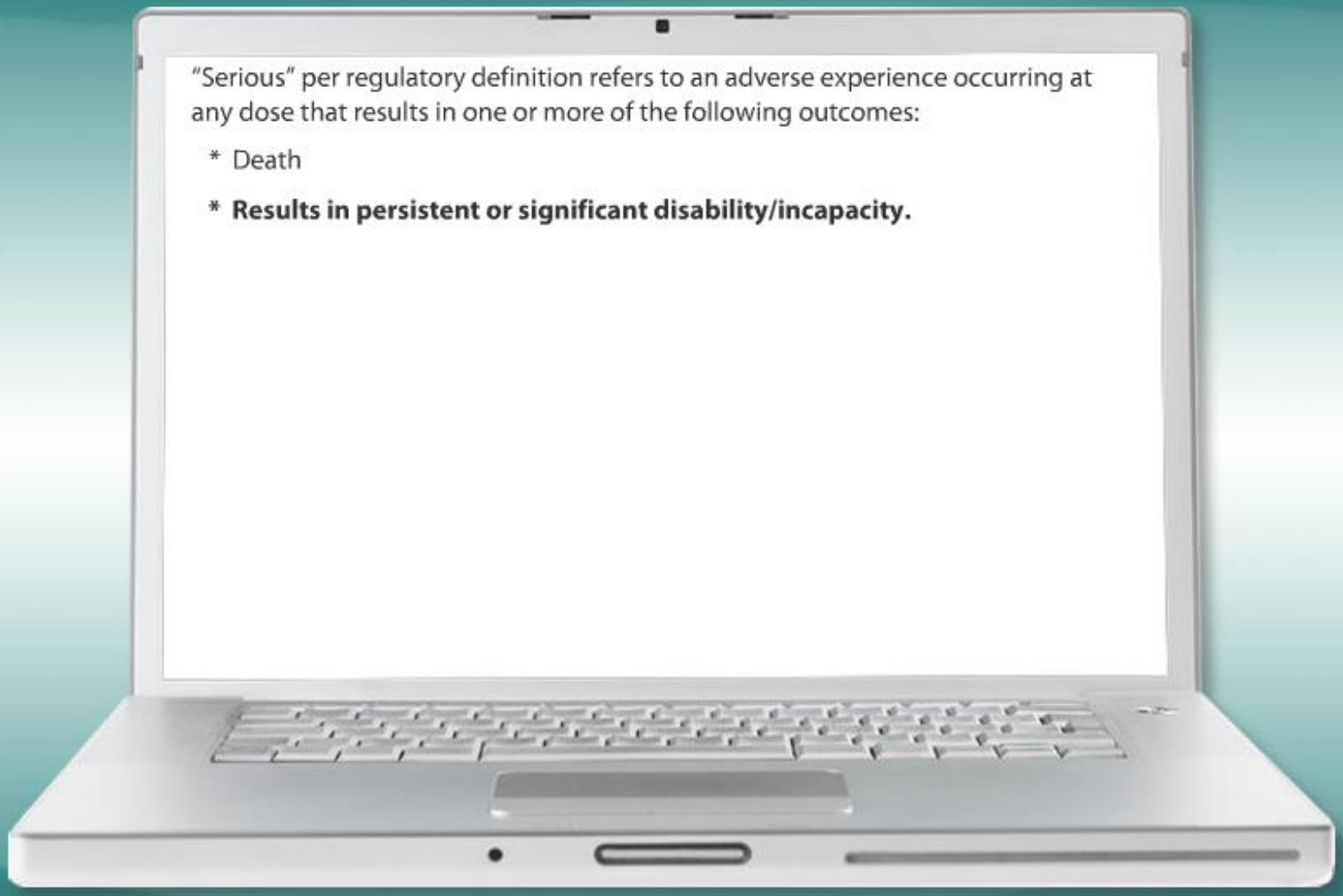

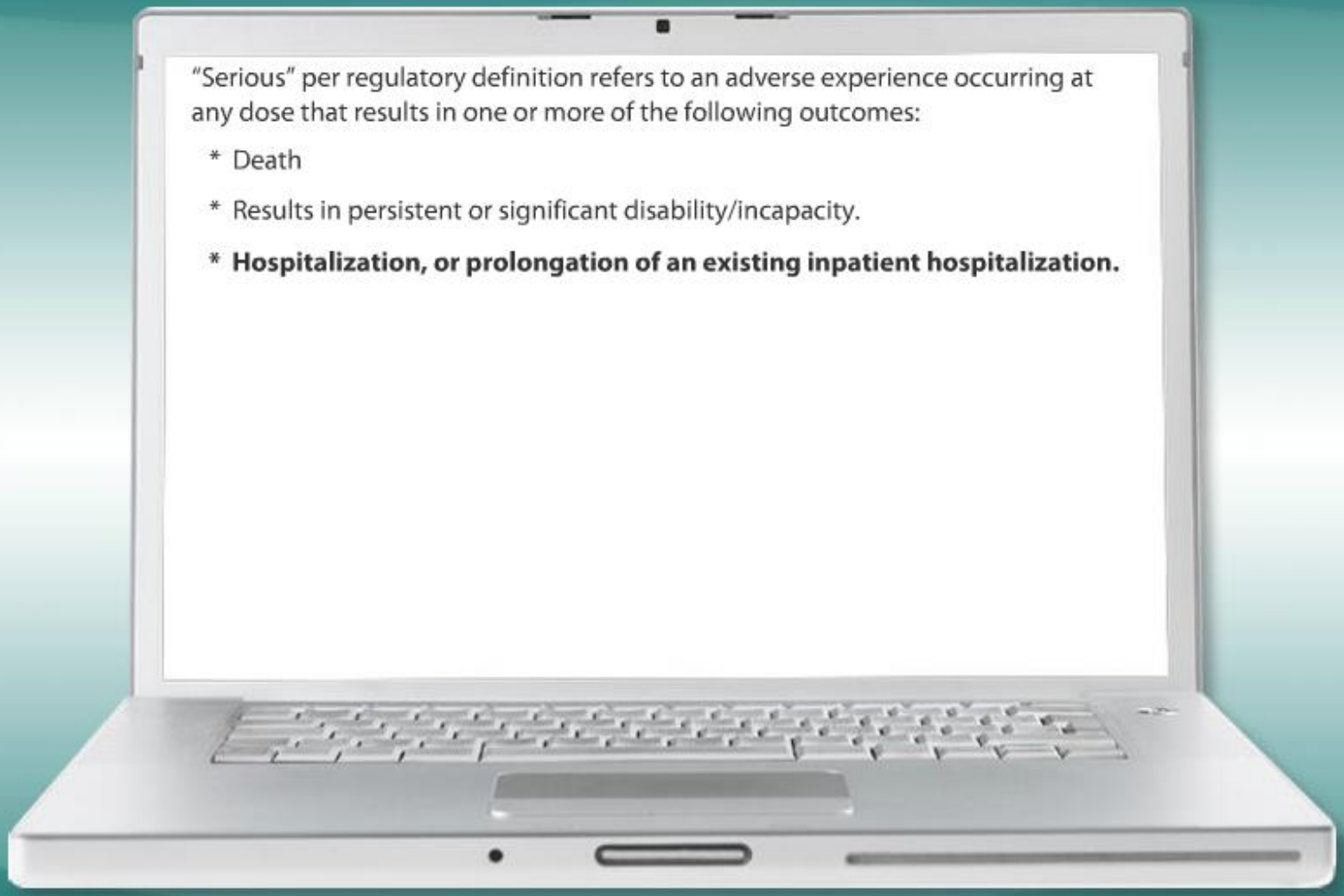

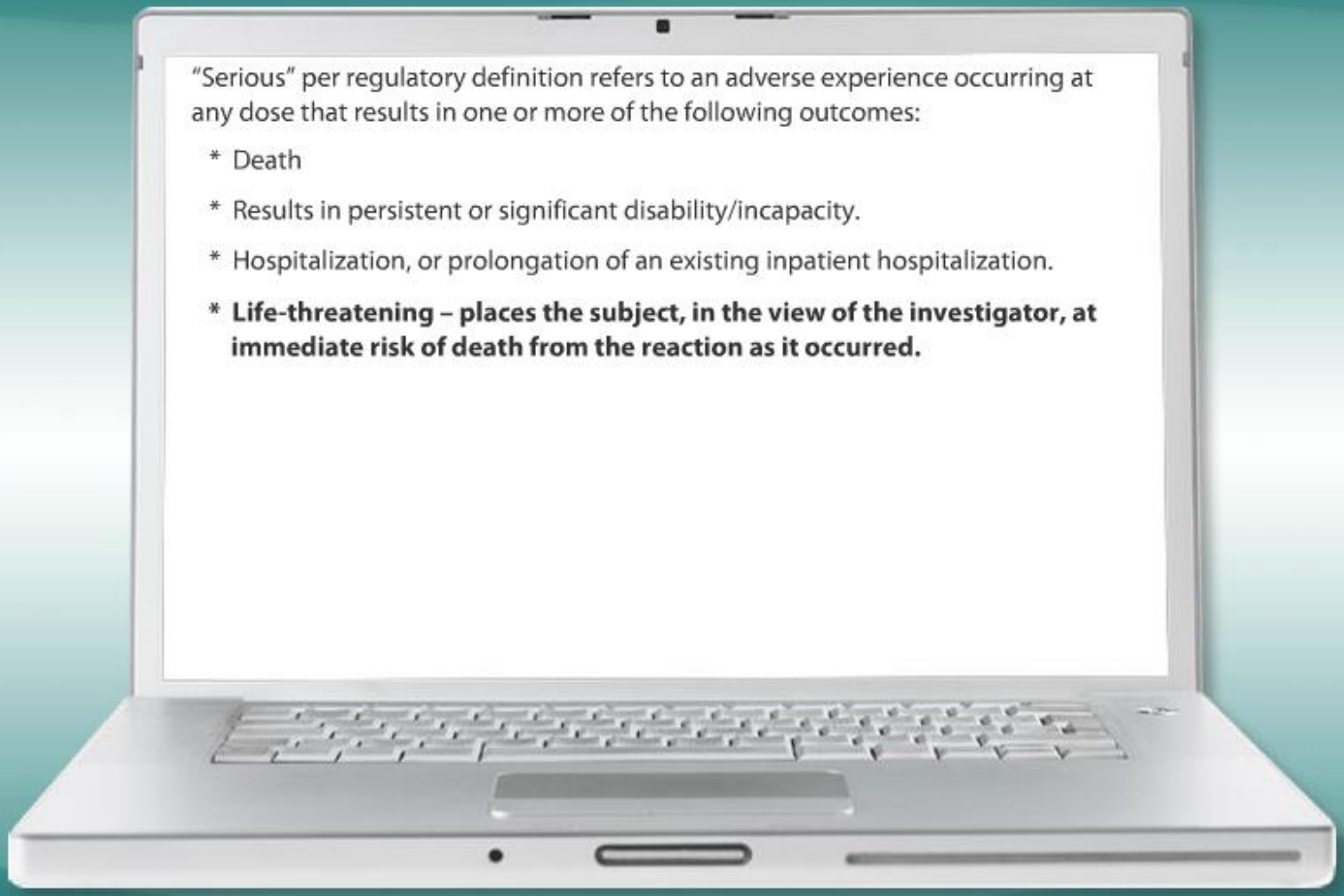

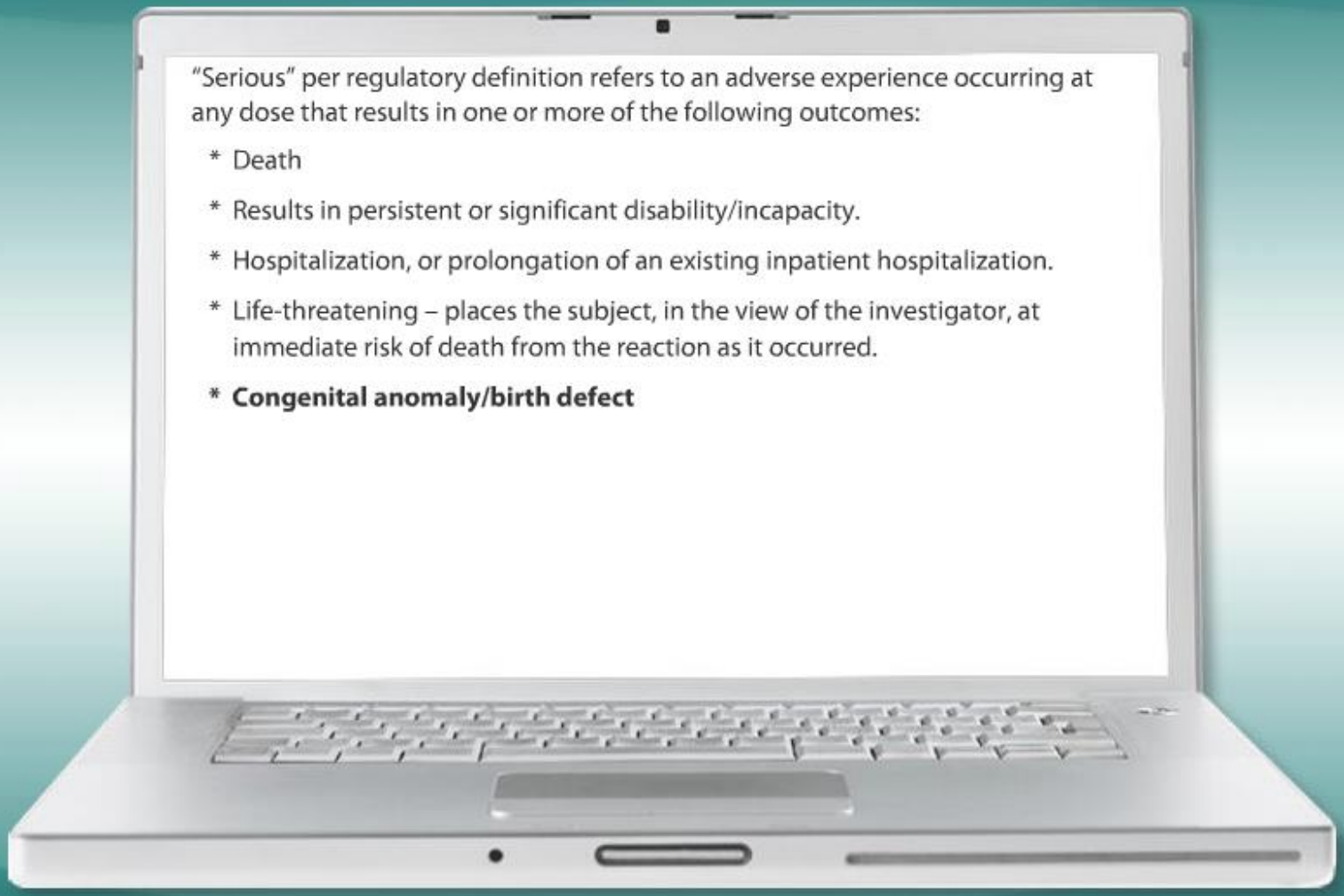

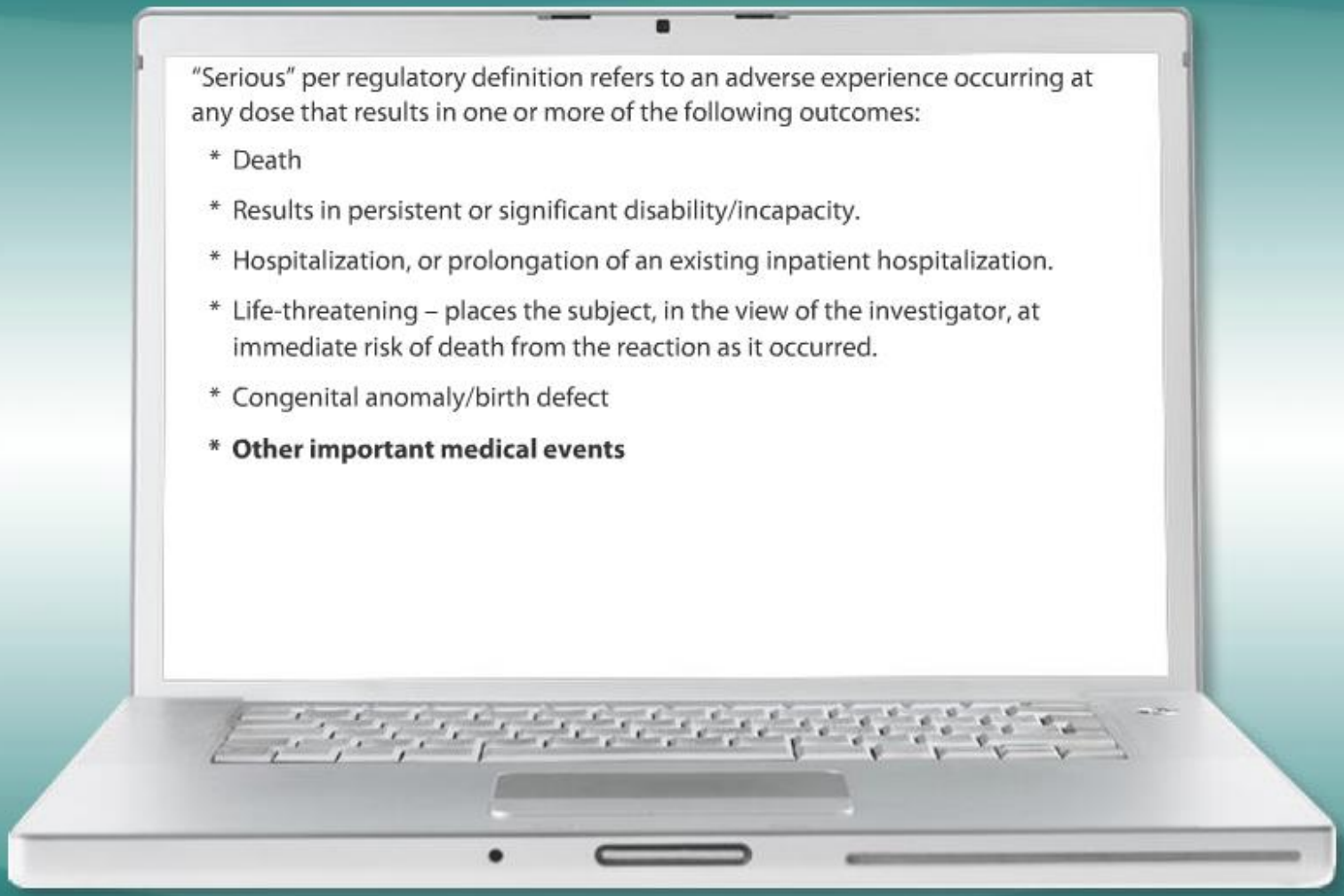

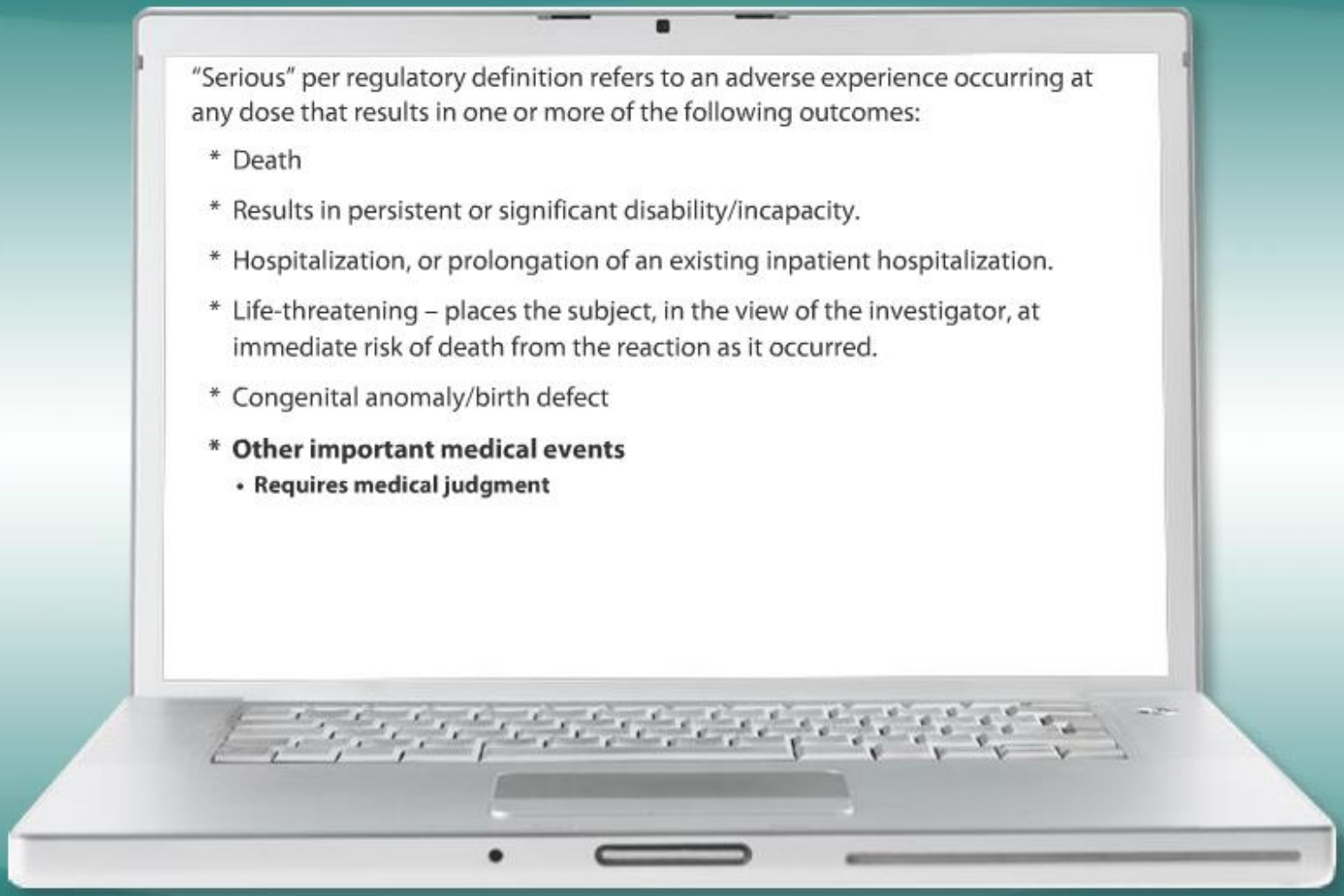

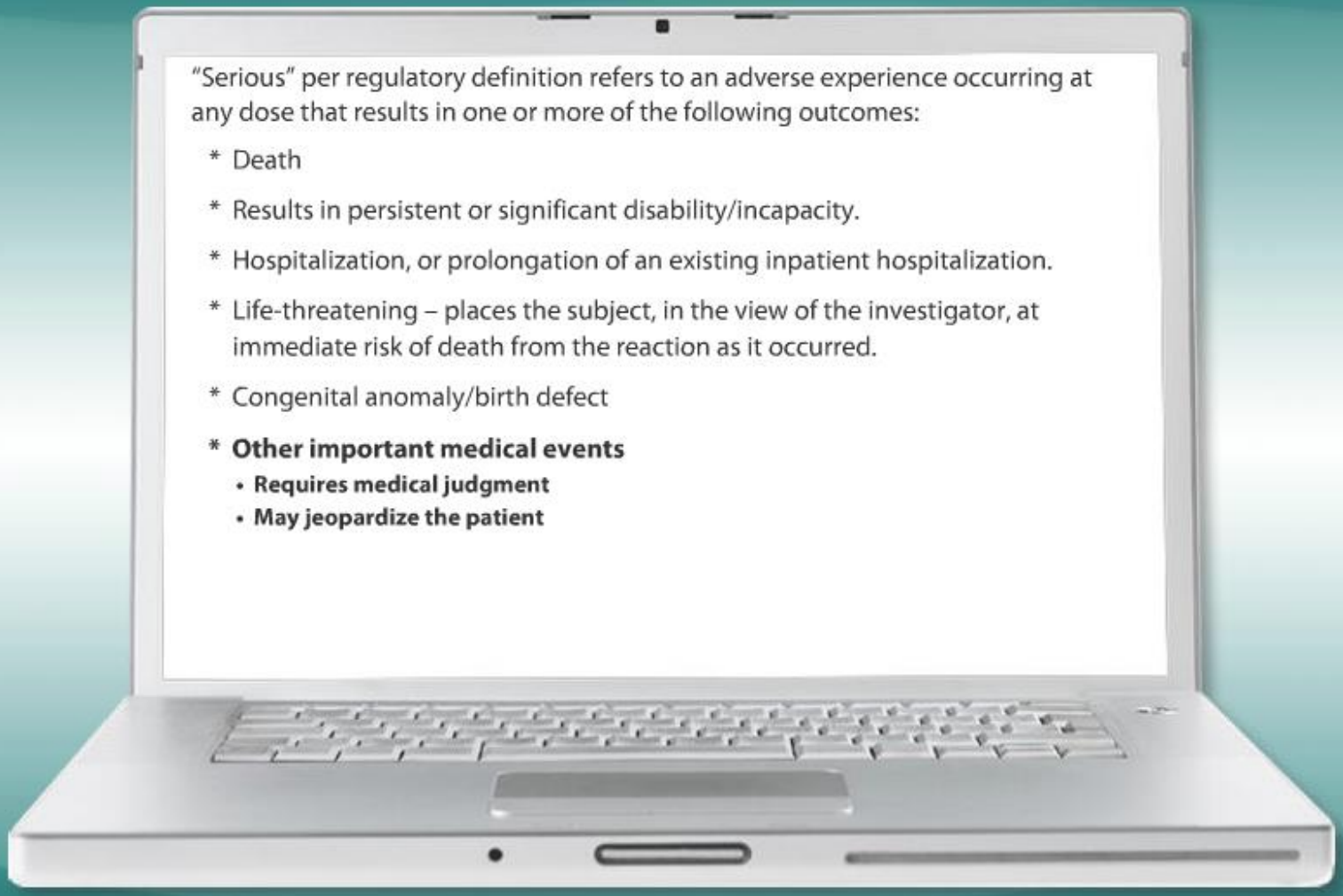

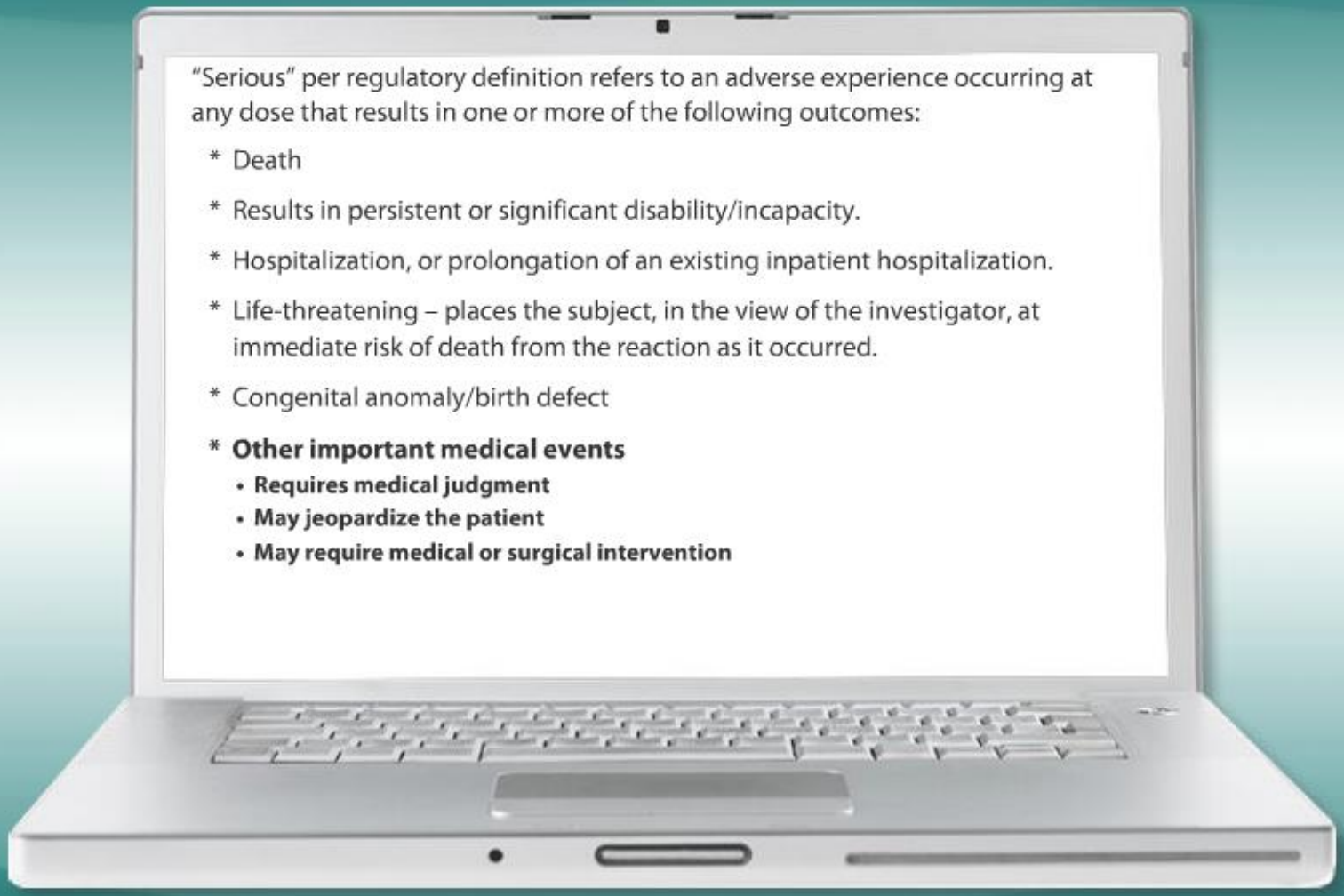

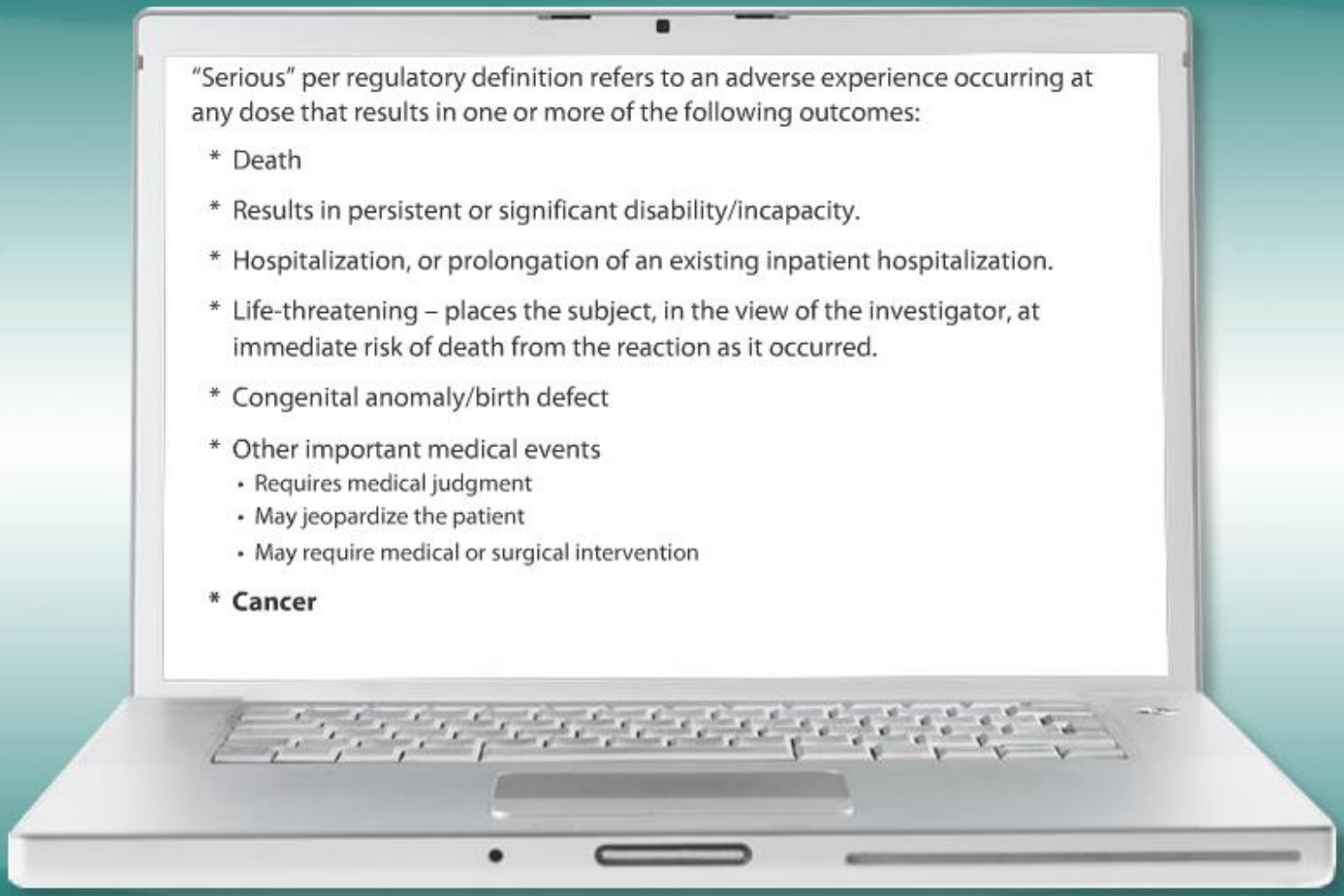

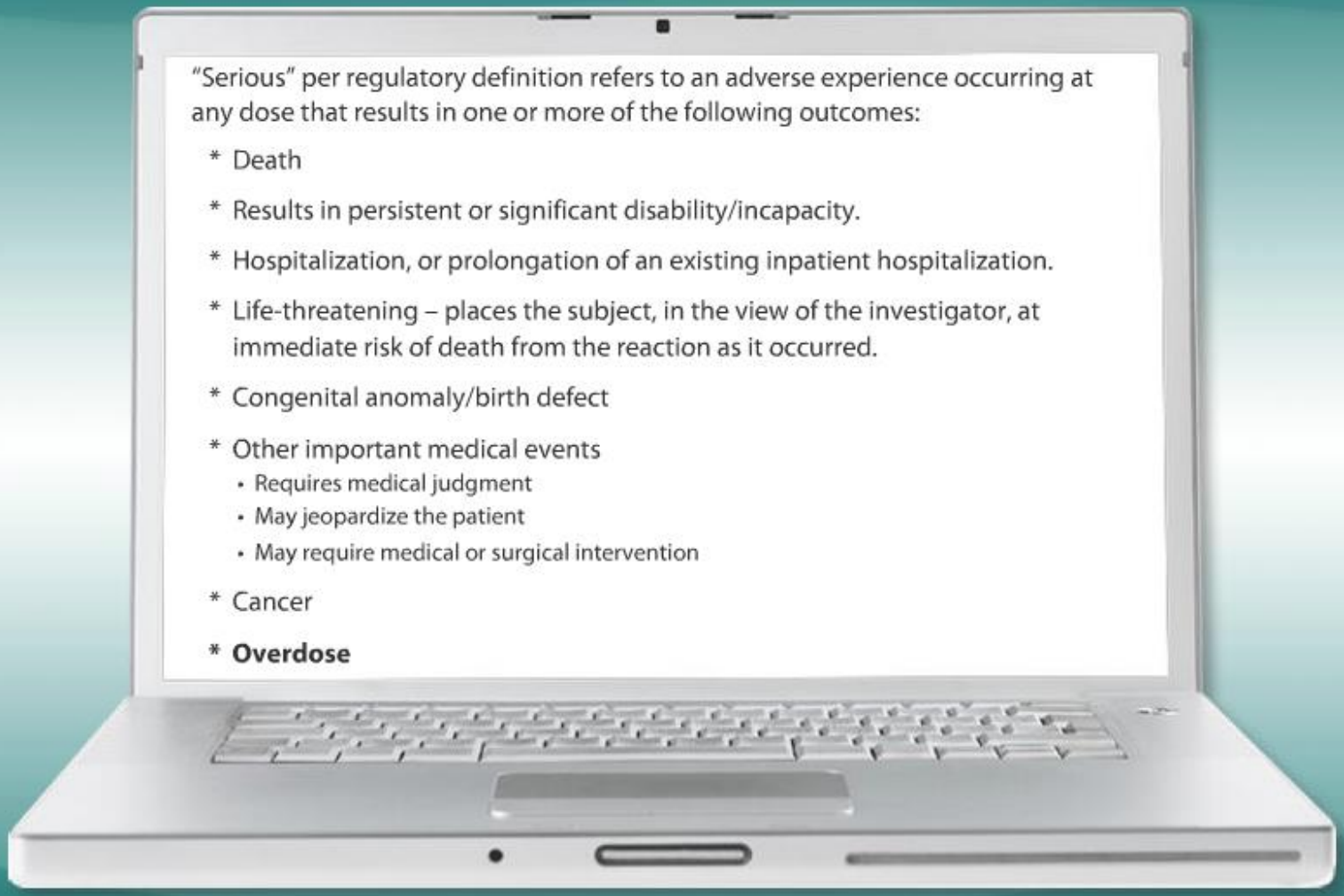

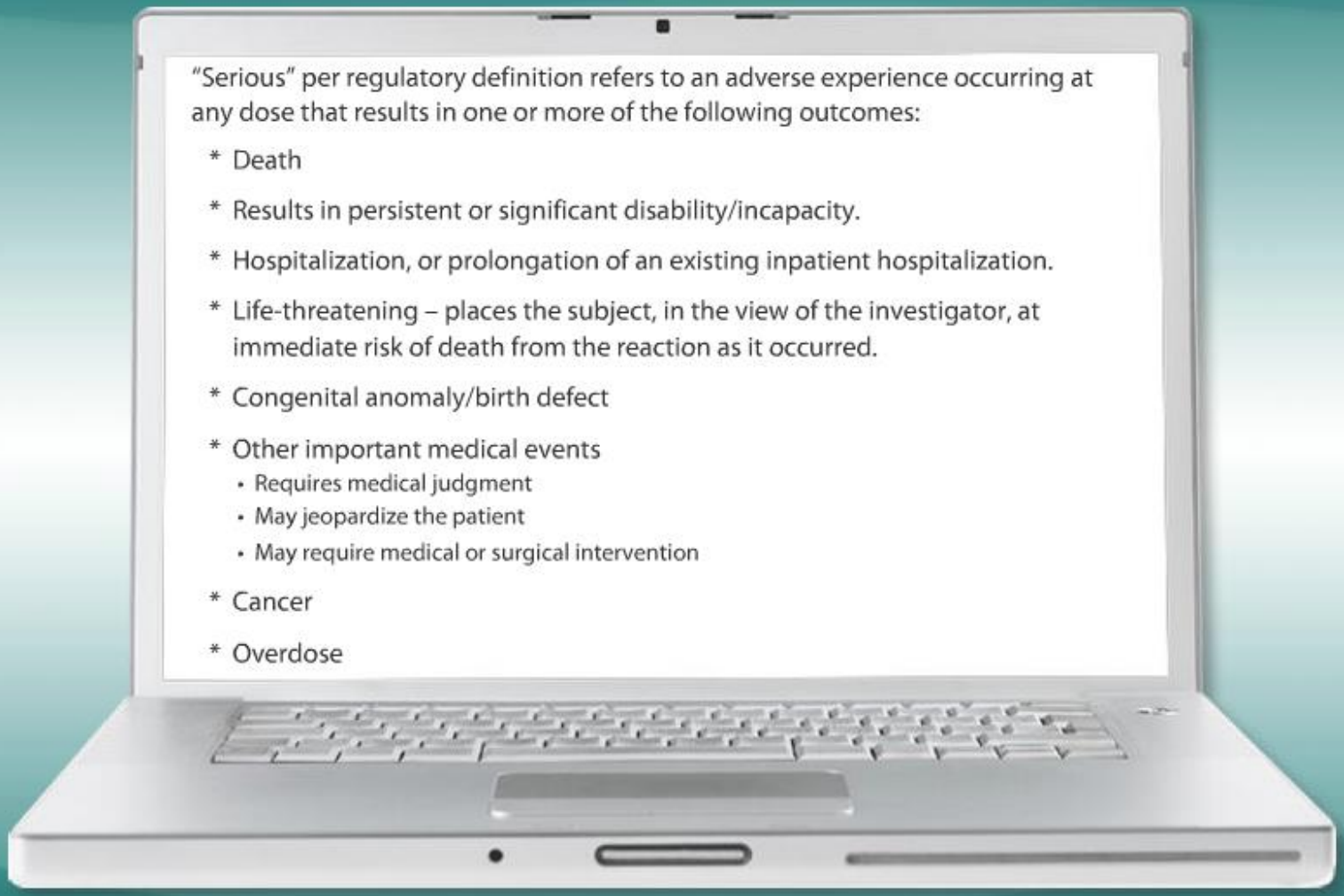

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- All phases of study

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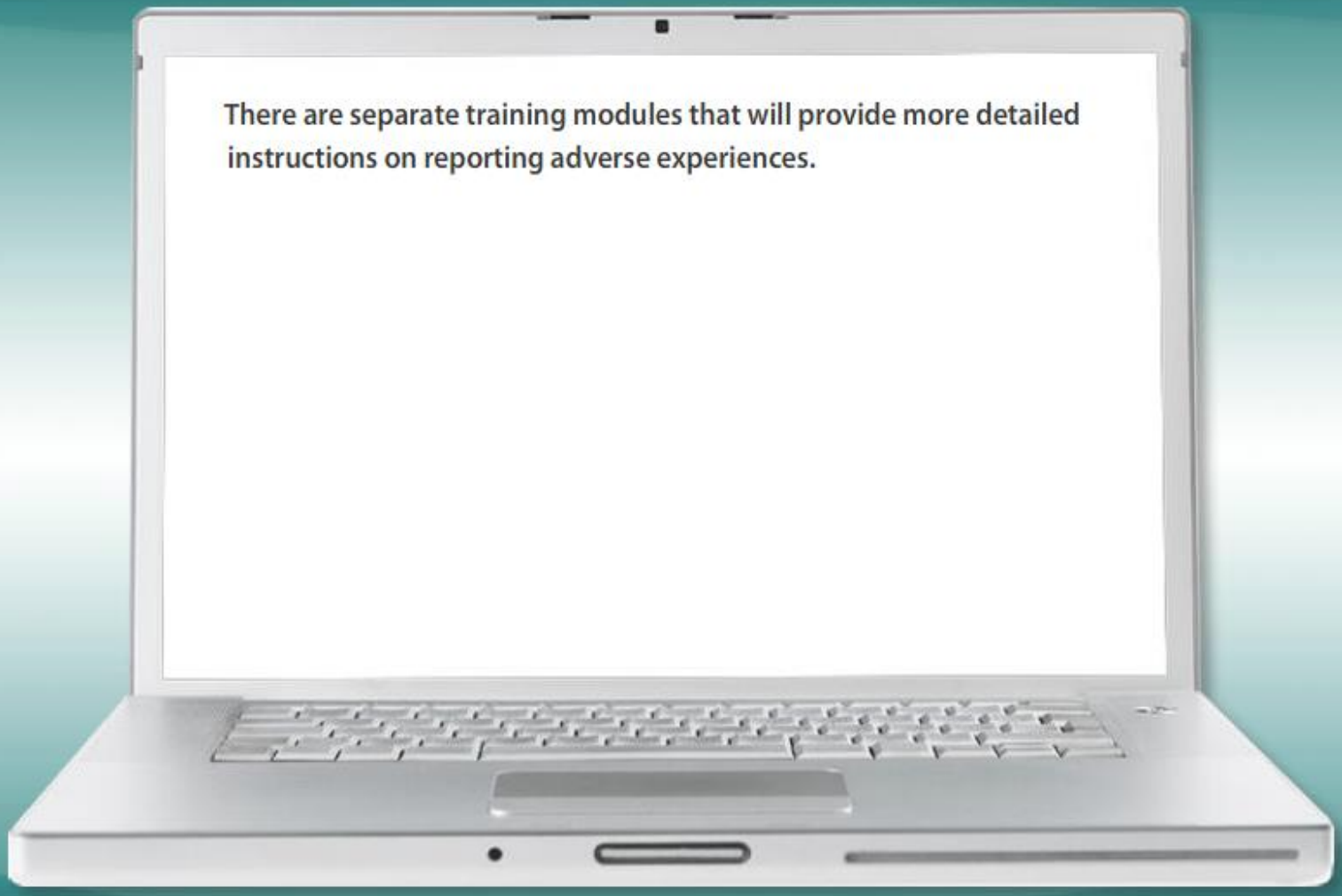
- Includes wash out or run-in periods



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Other Important Medical Event

1. Results in hospitalization
2. Life threatening
3. Results in death

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Serious Adverse Experience

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Scenario:
A subject enrolled in a hypertension study at your site is admitted to the hospital for an elective knee replacement that was scheduled before they enrolled into the clinical trial.

Is this hospitalization a serious adverse experience?

- ○ YES
- ○ NO

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A subject enrolled in a hypertension study at your site is admitted to the hospital for an elective knee replacement that was scheduled before they enrolled into the clinical trial.

Is this hospitalization a serious adverse experience?

- ○ YES
- ◉ NO

Feedback

That is correct, because the subject was already scheduled to have the knee replacement prior to enrolling in the study and there was no worsening of the preexisting condition during the study, this hospitalization would not be considered a serious adverse experience.

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Scenario:
A Computerized Axial Tomography (CT) Scan of the head was done and was found to be negative. The surgeon decided to keep the subject overnight for observation.

Is this event, loss of consciousness, considered a serious adverse experience?

- ○ YES
- ○ NO

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- (•) YES
- ( ) NO

Feedback

Correct , because this event prolonged the in-patient hospitalization this loss of consciousness would need to be reported within 24 hours of the investigative site personnel learning of the event.

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Mild: Easily tolerated

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Moderate: Interferes with normal activity

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Moderate: Interferes with normal activity

Severe: Unable to work or engage in usual activities

Let's make sure you understand these intensity classifications...

MILD	MODERATE	SEVERE

	A headache that resulted in the subject not being able to concentrate on reading so they took medication for the pain and decided to do filing where concentration was not as important.
	A throbbing headache that caused the subject to be nauseated stay home from work and remain in bed the entire day. The subject took 400 mg of Ibuprofen every 6 hours for 3 doses.
	A dull headache that went away within an hour and the subject continued their daily routine without doing anything differently.

Let's make sure you understand these intensity classifications...

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Let's review what criteria define an adverse experience as "serious".

- *Congenital anomaly/birth defect*
- *Outpatient surgical procedure*
- *Hospitalization/prolongation of an existing hospitalization*
- *Overdose*
- *Death*
- *Routine clinic visit*
- *Persistent or significant disability/incapacity*
- *Intravenous drug therapy*
- *Emergency Room visit*
- *Cancer*
- *Life-threatening*
- *Other medical important event*

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Take a few moments and see if you can match the guideline reference points to their definition.

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15 quality attributes that Merck requires investigators to address when reporting serious adverse experiences.

1. Supporting evaluations, signs and symptoms, diagnostic tests and/or results to corroborate each adverse experience term reported.
2. Information on the treatment provided for each adverse experience term reported.
3. "Resolution" of each adverse experience reported.
4. Causal relationship assessed by the investigator (PI or medically qualified designee).
5. Evidence that the SAE was closed (e.g. presence of the statement "no additional information is expected").
6. If SAE resulted in death, information on whether or not a post-mortem evaluation was performed, the cause of death and its possible relationship to study therapy.
7. If the patient was hospitalized, hospital discharge diagnosis provided.
8. The action taken as a result of each adverse experience term reported.
9. The daily dose of study therapy.
10. The route of administration of study therapy.
11. The indication for use of each suspect therapy.
12. Start date of study therapy.
13. Stop date or duration of study therapy.
14. Concomitant medication information.
15. De-challenge and/or re-challenge information.

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Pre-existing condition
≠
Adverse experience

Worsening of pre-existing condition = Adverse experience

Procedures
≠
Adverse experience

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History
- Type II Diabetes
- Post menopausal
- Migraine
- Gastro Esophageal Reflux Disease (GERD)

Mrs. Santo was screened and randomized to a Merck diabetic study. Review the data points collected during her visits to determine whether any of them should be reported as an adverse experience.

Do any of the data points indicate an adverse experience?

Her vital signs:	**Screening 7/11/08**	**Visit 1 7/25/08**	Yes	No	Need more information
Blood pressure	122/74 mmHg	124/74 mmHg	○	○	○
Respiratory rate per minute	22	22	○	○	○
Pulse	64 bpm	66 bpm	○	○	○
Weight	87.8 kg	87.5 kg	○	○	○
Height	165.1 cm	not required	○	○	○
		Study coordinator inquired if subject had any health care visits since baseline visit and, if so, what was the purpose of the visit?			
doctor		Yes Dental appointment	○	○	○
clinic		No	○	○	○
emergency room		No	○	○	○
hospital visits		No	○	○	○
Concomitant Medications	1) Rizatriptan 5mg prn	1) Rizatriptan 5mg prn - not needed	○	○	○
	2) Metformin 500mg bid	2) Metformin 500 mg bid	○	○	○
	3) Lansoprazole 15mg prn	3) Lansoprazole 15 mg 7/20/08 once only	○	○	○
		4) Ibuprofen 1200mg daily from 7/14 - 7/16/08.	○	○	○
		5) Study Medication MK-XXXX or placebo 1 tab q am	○	○	○

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Now, with additional information available is the data point an adverse experience?

	Visit 1 **7/25/08**	**If more information was required from previous response - here is the updated data.**	**Yes**	**No**
	Study coordinator inquired if subject had any health care visits since baseline visit and, if so, what was the purpose of the visit?			
doctor	Yes Dental appointment	Visit was for routine teeth cleaning	○	○
Concomitant Medications	3) Lansoprazole 15 mg 7/20/08 once only	3) Subject reported that on 7/20 she went out to dinner with friends and ate very spicy food. Before she left home she took lansoprazole as prophylaxis for her occasional gastro esophageal reflux disease (GERD). Subject did not have any problems with GERD.	○	○
	4) Ibuprofen 1200mg daily from 7/14 - 7/16/08	4) Subject took ibuprofen because of lower back pain that occurred after working in the garden. She believed it was simply a sore muscle, as the pain resolved in 2 days by using a heating pad and taking the Ibuprofen. She did not seek any medical attention for the back pain.	○	○

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✓ **Use of lansoprazole not related to an adverse experience as subject has documented history of GERD and did not have any new or different problems.**

✓ **Non-serious adverse experience – lower back pain**

You see a study patient that has a documented history of bilateral osteoarthritis (OA) of the knee who reported at baseline that he uses over-the-counter (OTC) acetaminophen (paracetamol) to treat periodic osteoarthritis flares.

The patient is in for a routine visit and reports to the study coordinator that during the previous week his osteoarthritis knee pain had increased as it always does when its rains and he took his usual acetaminophen (paracetamol) 650mg four times daily on Monday, Tuesday and Wednesday - with good results.

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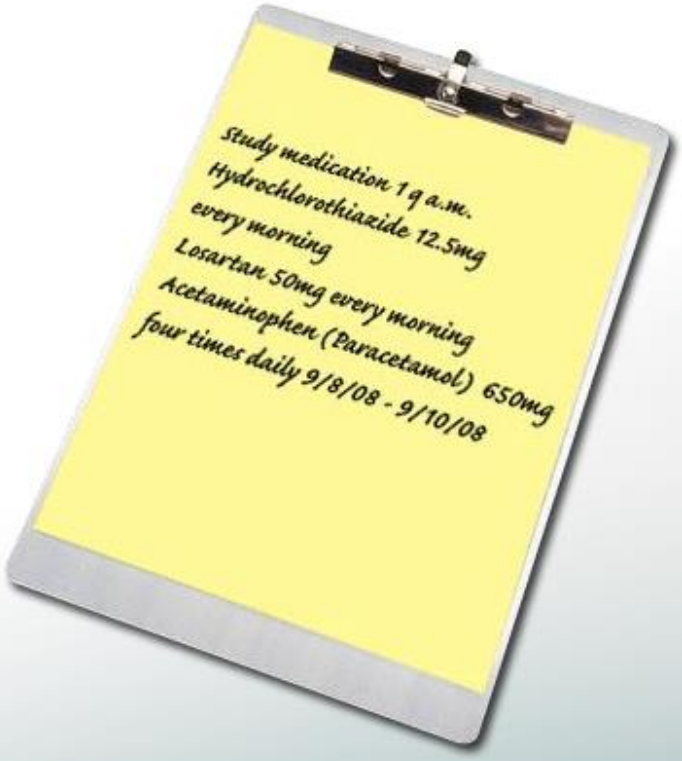

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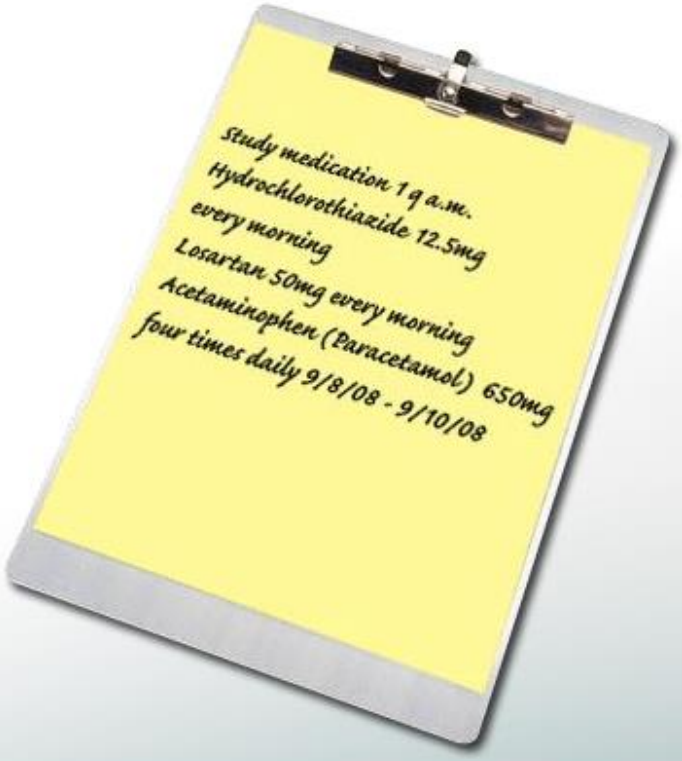

Should this episode of osteoarthritis be captured as an adverse experience?

Yes

No

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According to the subject's report there was no worsening of his baseline condition. The subject reported that the flare occurred "as it always does when it rains." He took his usual treatment and dosage of acetaminophen (paracetamol) and had good results & the pain subsided.

Should this episode of osteoarthritis be captured as an adverse experience?

Yes

No

During a subsequent study visit, the subject reported that he had another flare of his osteoarthritis, he took acetaminophen (paracetamol) but it did not provide much relief. He reported having severe difficulty even walking because his knees were stiff and painful which was unlike his usual flare of osteoarthritis.

He went to his primary care physician who put him on naproxen 500mg every 12 hours that he took for 6 days.

He reported that the pain and stiffness started to improve after being on the naproxen for 2 days and by the 6th day the pain and stiffness were resolved.

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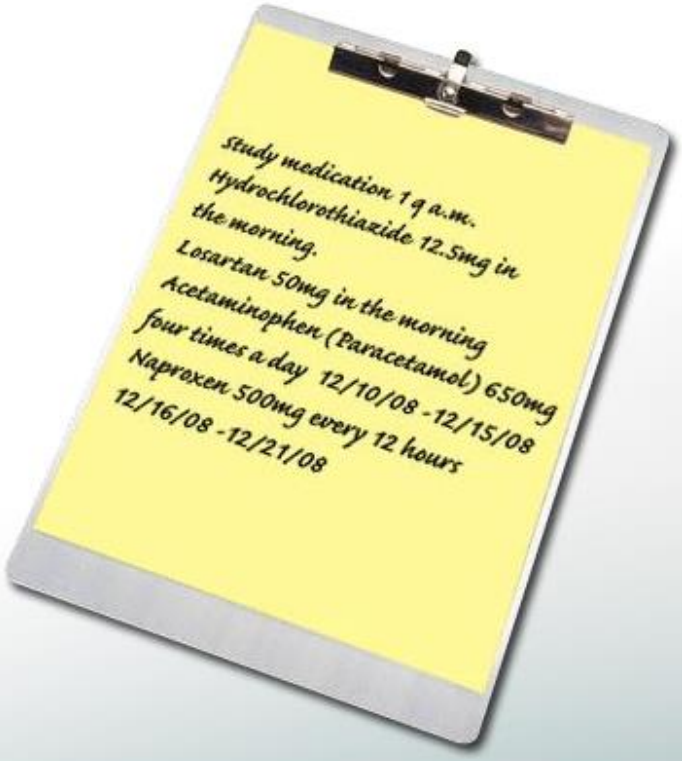

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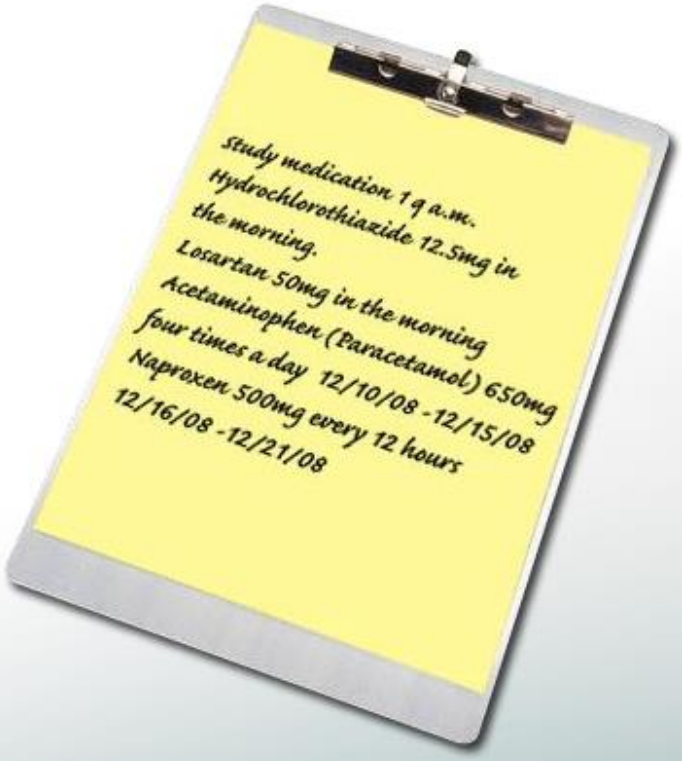

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Should this episode of osteoarthritis be captured as an adverse experience?

Yes

No

Let's discuss how you would handle this adverse experience.

How would this adverse experience be classified and when would it be reported to Merck/MSD?

Serious Adverse Experience.
Report to Merck/MSD within 24 hours of learning about the event.

Serious Adverse Experience.
Report to Merck/MSD within 5 days of learning of event.

Non-Serious Adverse Experience.
Report to Merck/MSD within 24 business days.

Non-Serious Adverse Experience.
Report to Merck/MSD when (e)Case Report Forms are routinely submitted.

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The pain and stiffness were worse than reported at the beginning of the study. This would be a worsening of a pre-existing condition.

Dr. Wright, who is the principal investigator for the Merck/MSD hypertension study, receives a telephone call from the hospital emergency room regarding one of her clinic patients, Mrs. Sydney Clark who is also participating in the hypertension study.

The emergency room physician, Dr. Yen reports that the Mrs. Clark presented with shortness of breath, sweating, severe chest pain (9/10). The chest pain has lessened, but is still present, her electrocardiogram shows elevated ST segment and significant Q wave. Creatine kinase (CK) and Troponin blood levels were drawn and the results are pending. Mrs. Clark's vital signs have been unstable.

Mrs. Clark was given an aspirin to chew, intravenous morphine and oxygen via nasal cannula. She was started on a nitroglycerin drip and the chest pain has lessened, but is still a 6/10.

Dr. Steven, the interventionalist cardiologist believes the patient is experiencing a myocardial infarction. Dr. Steven is on her way to the hospital to evaluate Mrs. Clark. Dr. Steven has the cardiac catheterization lab on stand-by. The patient has been admitted as an inpatient to the hospital in the coronary care unit.

Saturday morning, 8:30am

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Based on the information available is there a reportable event, if so, what type of event?

Yes - Serious Adverse Experience

There is not enough information available to make a determination.

No - because the subject has a previous history of cardiovascular disease this does not fit the definition of an adverse experience.

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Mrs. Clark was admitted as an inpatient to the coronary care unit which meets the serious adverse experience criteria of hospitalization.

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Is there any action required of Dr. Wright with regard to reporting this serious adverse experience to Merck/MSD?

- No Action
- YES Action required

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What action would Dr. Wright need to take?

Within 24 hours, Dr. Wright or her designee would need to report the event to Merck/MSD with the currently available information (at a minimum, they will need to provide the protocol number, the subject allocation number, the investigational medication, adverse experience, as well as name of person reporting event).

By Monday morning report the event to the sponsor including the subject identifiers, the medication under study, adverse event or outcome, as well as name of person reporting event).

Obtain the subject's medical records and when all information is available report the event to the sponsor.

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That means by 8:30 a.m. tomorrow morning (Sunday) Dr. Wright will need to have notified Merck/MSD of the event. Remember you must provide the event term, in this case myocardial infarction and not just 'hospitalization.' Updates will need to be provided as additional information becomes available.

Questions

If you have any questions please use the ‘Ask Question’ feature at the bottom of the presentation player.

ASK QUESTION

Thank you for your attention.