ADVERSE EVENT REPORTING

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Reporting Adverse Events

- Adverse Events (AEs) are ". . . any **untoward** medical occurrence in a subject that was not previously identified which does not necessarily have a causal relationship to the study drug…"
- Events existing prior to randomization should not be reported as AEs, unless there is a change in severity
- Pre-existing conditions that are discovered after randomization are not adverse events. These should be documented as medical history.
- Abnormal lab values that are considered to be clinical significant by the site investigator are adverse events

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Reporting Adverse Events

- Adverse Events are reported on Adverse Event CRF
- 1 AE per CRF
- Report the diagnosis, not the symptoms:
  Fever, cough, chest pain, crackles = pneumonia
- Avoid abbreviations/colloquialisms

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Reporting Adverse Events

- Death, surgery, intubation, etc. are not adverse events. They are outcomes of adverse events
- All AEs will be centrally coded verbatim using MedDRA
- AEs that can't be coded will be queried

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Reporting Adverse Events

Report AEs from Study Treatment through 24 Hours post-treatment

Report only SAEs from Study Treatment through End of Study

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Reporting Adverse Events

Serious Adverse Events are:

- Fatal,
- Life-Threatening,
- Result in hospitalization/prolongation of hospitalization- excluding optional, pre-planned surgery
- Result in disability/congenital anomaly, or
- Require intervention to prevent permanent impairment or damage

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Data Entry Time Lines for AEs

- Non-serious AEs must be entered and **submitted** into WebDCU™ within 5 days of data collection.

- SAEs must be entered and **submitted** into WebDCU™ within **24 hours** of discovery

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Reporting SAEs

SAEs require additional information

to be submitted on the AE CRF:

1. Detailed description of the event
2. Relevant tests/laboratory data
3. Relevant history and pre-existing conditions
4. Concomitant meds

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Reporting SAEs

- These narratives assist the Independent Medical
  Safety Monitor in reviewing the event

- Narratives are pre-populated into the MedWatch form, if expedited reporting is required

- Do not identify any subject, physician, or institution by name.

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Reporting SAEs

- Site data enters and submits AE CRF into WebDCU™
- Automatic e-mail notifications to Site Manager (SM) and Internal Quality Reviewer (IQR)
- If AE data is sufficient, an automatic email notification will be sent to the Independent Medical Safety Monitor (IMSM)
- IMSM blindly reviews the event and indicates whether the event is serious, unexpected, and study drug related
- SM closes review process

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MedWatch Reports

- FDA requires expedited reporting for

  AEs that are serious, unexpected, and study drug related

- If the IMSM determines that the SAE is serious, unexpected, and related to study drug, WebDCU™ generates an pre-populated MedWatch form and sends an automatic email notification to the site coordinator.

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MedWatch Reports

- Spoke staff completes the MedWatch
- The SM submits MedWatch to FDA
- The SM notifies sites of MedWatch posting on WebDCU
- Site PIs are responsible for reporting the SAE to their IRB according to local requirements

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MedWatch Reports

Fatal or life threatening SAEs:

- Initial report due within 7 days of discovery
- Complete report due within 15 days of discovery

Non-fatal and non-life threatening SAEs:

- Initial report due within 15 days of discovery

Follow Up Reporting

- PI responsible for obtaining any follow-up information and submitting that data into WebDCU™ as soon as it becomes available.

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Pop Quiz!

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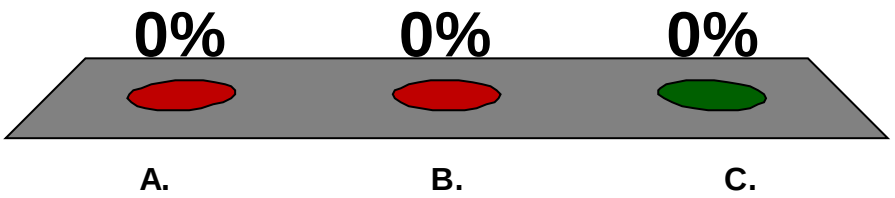
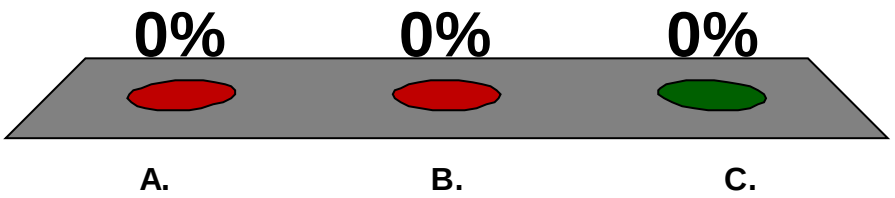
How do you report a SAE?

A. Call the ESETT Hotline
B. Call the ESETT hotline and data enter the AE CRF
C. Data enter and submit the AE CRF



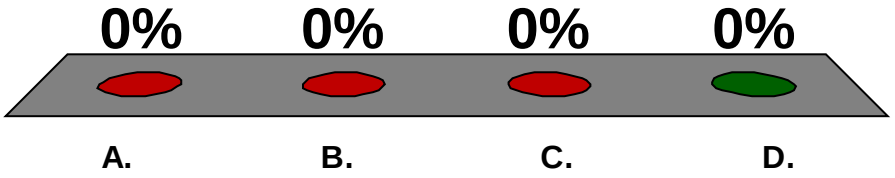
What are the timelines for submission of SAE data?

A. 3 days from first knowledge of the event
B. 5 days from first knowledge of the event
C. 24 hours from first knowledge of the event



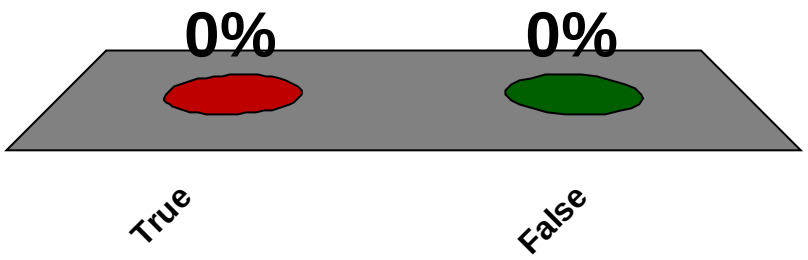
Which AEs must be reported on a MedWatch?

A. Serious AEs
B. Serious AEs that result in death
C. Serious AEs that are study related
D. Serious AEs that are study related and unexpected

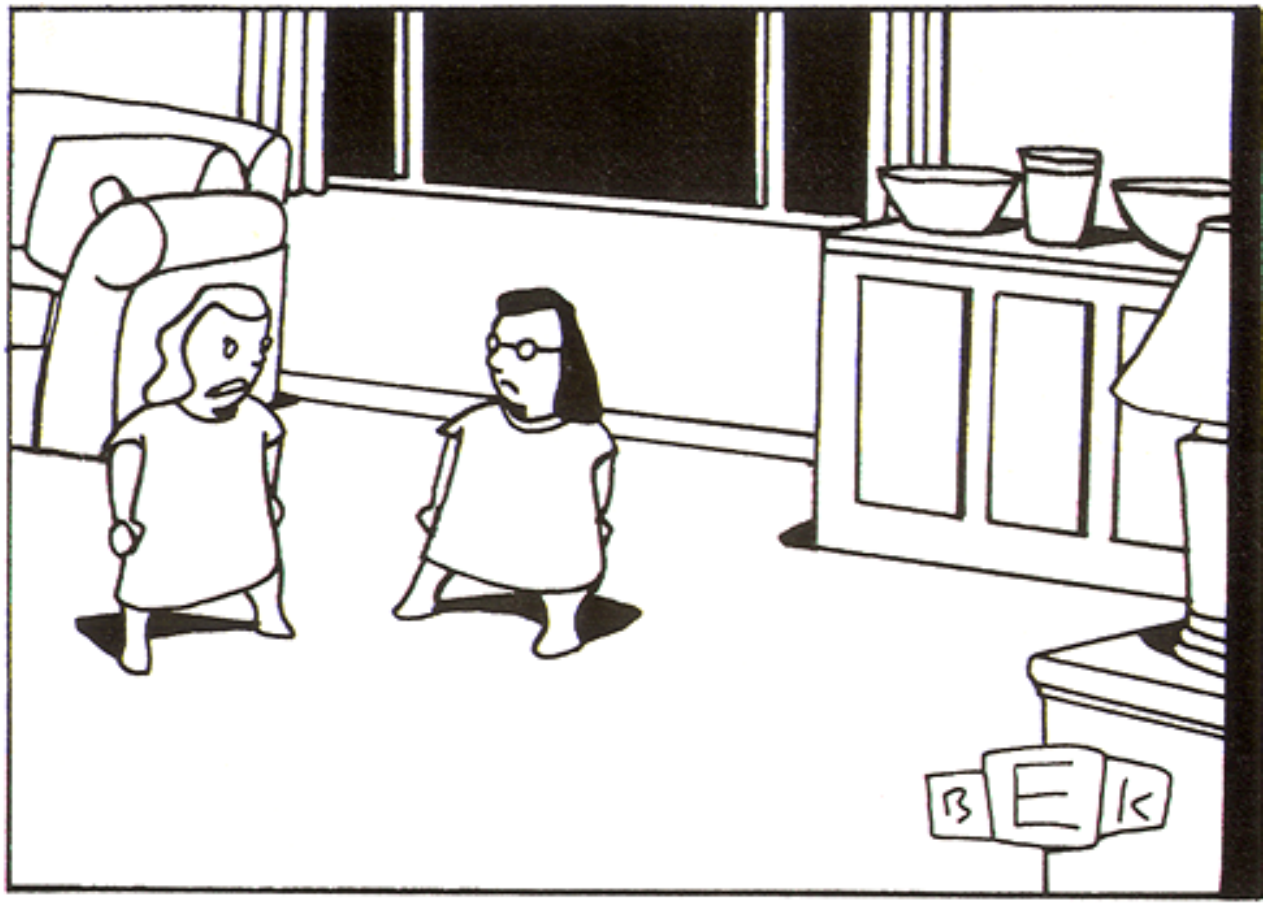


‘Death’ is a valid adverse event name

A. True
B. False



Adverse Events and Serious Adverse Events



"Try falling down and scraping your knee. Then you can talk to me about pain."

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Adverse Events –

- Do not report events EXISTING PRIOR to randomization
  (unless there is a change in severity)

- Report the DIAGNOSIS, not the symptoms:
  Fever, cough, chest pain, crackles = pneumonia

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Relatedness

Not Related
- The timing is wrong and there was clearly another cause

Unlikely (both of the following, but timing doesn't matter)
- Another cause is possible
- Not something the intervention is known to cause

Reasonable Possibly (2 of 3)
- Timing is suggestive.
- Not readily caused by something else
- This is something the intervention is known to cause.

Definitely (must have all 3)
- Timing suggests intervention caused the problem.
- No other possible cause.
- This is something the intervention is known to cause.

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A 52 yo was found seizing, was refractory to benzo's in the ED and was appropriately enrolled . Her convulsions stop after study drug administration. After recovering from her post ictal state she complains of a severe headache. CT shows a subarachnoid hemorrhage. After diagnostic angiography she is admitted to the ICU to await surgery. 14 hours after admission her neurological condition deteriorates and repeat CT shows a massive re-bleed, which is fatal 2 hours later.

Adverse event? Yes / No

Serious? Yes / No

Expected? Yes / No

Related to study? A. Not related

B. Unlikely

C. Reasonable Possibly

D. Definitely

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A 14 yo with epilepsy developed refractory status and was appropriately enrolled . In the ED he stops convulsing, but remains unresponsive. His respirations are shallow and he making some snoring noises. The ED places a nasopharyngeal airway. Subsequently the patient becomes more alert and 15 minutes later the nasal trumpet is removed.

Adverse event?	Yes / No
Serious?	Yes / No
Expected?	Yes / No
Related to study?	A. Not related
	B. Unlikely
	C. Reasonable Possibly
	D. Definitely

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Continuing with the same case…. After initially starting to wake up, the 14 yo begins convulsing again. He is treated with IV phenobarbital, and then intubated and treated with a propofol drip. He is admitted to the ICU for continuous EEG monitoring.

Adverse event?	Yes / No
Serious?	Yes / No
Expected?	Yes / No
Related to study?	A. Not related
	B. Unlikely
	C. Reasonable Possibly
	D. Definitely

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A 24 yo is appropriately enrolled. Her convulsions stop after study drug administration, and she wakes up after a post-ictal period. Shortly after admission she complains of mild to moderate nausea, but declines an antiemetic when it is offered to her.

Adverse event? Yes / No

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Ok, let's change it just a little…. A 24 yo is appropriately enrolled. Her convulsions stop after study drug administration, and she wakes up after a post-ictal period. 6 hours after admission she complains of mild to moderate nausea, and is treated with Zofran, after which her nausea resolves.

Adverse event?	Yes / No
Serious?	Yes / No
Expected?	Yes / No
Related to study?	A. Not related
	B. Unlikely
	C. Reasonable Possibly
	D. Definitely

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"I just have to create a few loose ends for other people to clear up, and then I can out of here."

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Write good SAE narratives

Be concise but complete (not comprehensive)

- Include only the pertinent PMH and HPI
- Describe the event
- Describe the response
- Describe the outcome
- And say when each of those happened

Look for and respond to queries promptly

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Sample narrative

A 83 year old female with a history of epilepsy was found seizing and was appropriately enrolled at 18:05 on 3/10/09. In the ED at 20:22 she was awake and conversant. At 21:10 she had another generalized seizure and was treated with lorazepam 2 mg IV with termination of her seizure at 21:14. Her phenytoin level subsequently was reported to be 5 . At 21:25 she was given phenytoin 1 g IV. At admission at 22:50 she was again awake and conversant.

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Sample narrative

A 83 year old female with a history of epilepsy was found seizing and was appropriately enrolled at 18:05 on 3/10/09. No respiratory distress or hypoxia was noted in the ED. Pulse ox 97% at 22:00 before admission. On 3/11/09 at 16:00, she was noted to be short of breath with a pulse ox of 88% on room air. At 16:15 supplemental oxygen was administered at 4 LPM and pulse ox was 93%. Chest x-ray at 17:11 showed RLL infiltrate suggestive of aspiration. Respiratory distress increased and at 23:20 she was transferred to the ICU and endotracheally intubated.

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Narrative template

A [age] year old [male/female] was found seizing on [date] at [time] and was enrolled in ESETT. The patient [stopped/did not stop] seizing after study drug administration. The patient subsequently underwent endotracheal intubation for respiratory depression [in the ED/on the ward/in the ICU] at [time]. The patient [was/was not] still thought to be seizing at the time of intubation.

[The patient was subsequently extubated on [date].]

[The patient remained intubated as of [date] because of [suspected etiology].]

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Narrative template completed

Respiratory Depression

A 38 year old male with a history of seizures, was found seizing and was enrolled in ESETT at approximately 20:45 on 9/1/2009. The patient did stop convulsing after study drug administration. He subsequently underwent endotracheal intubation for respiratory depression in the ED at 21:20. The patient was not thought to be seizing at the time of intubation, but was felt to have respiratory depression from the combination of alcohol intoxication, and benzodiazepines. The patient was treated with propofol and admitted to the ICU. The patient was subsequently extubated on 9/2/2009.

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