# ESETT OUTCOMES

Investigator Kick-off Meeting

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Established Status Epilepticus Treatment Trial

# Primary objective

- The primary objective is to determine the most effective and/or the least effective treatment of benzodiazepine-refractory status epilepticus (SE) among patients older than 2 years. There are three active treatment arms being compared: fosphenytoin (FOS), levetiracetam (LEV), and valproic acid (VPA).

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# Primary outcome

- The  primary outcome is clinical cessation of status epilepticus, determined by the absence of clinically apparent seizures and improving responsiveness, at 60 minutes after the start of study drug infusion, without the use of additional anti-seizure medication.

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# Secondary objectives

- determination of the relative safety of the treatment arms on defined safety outcomes and all adverse events,
- analysis of secondary efficacy outcomes,
- evaluation of both effectiveness and safety in the pediatric subpopulation.

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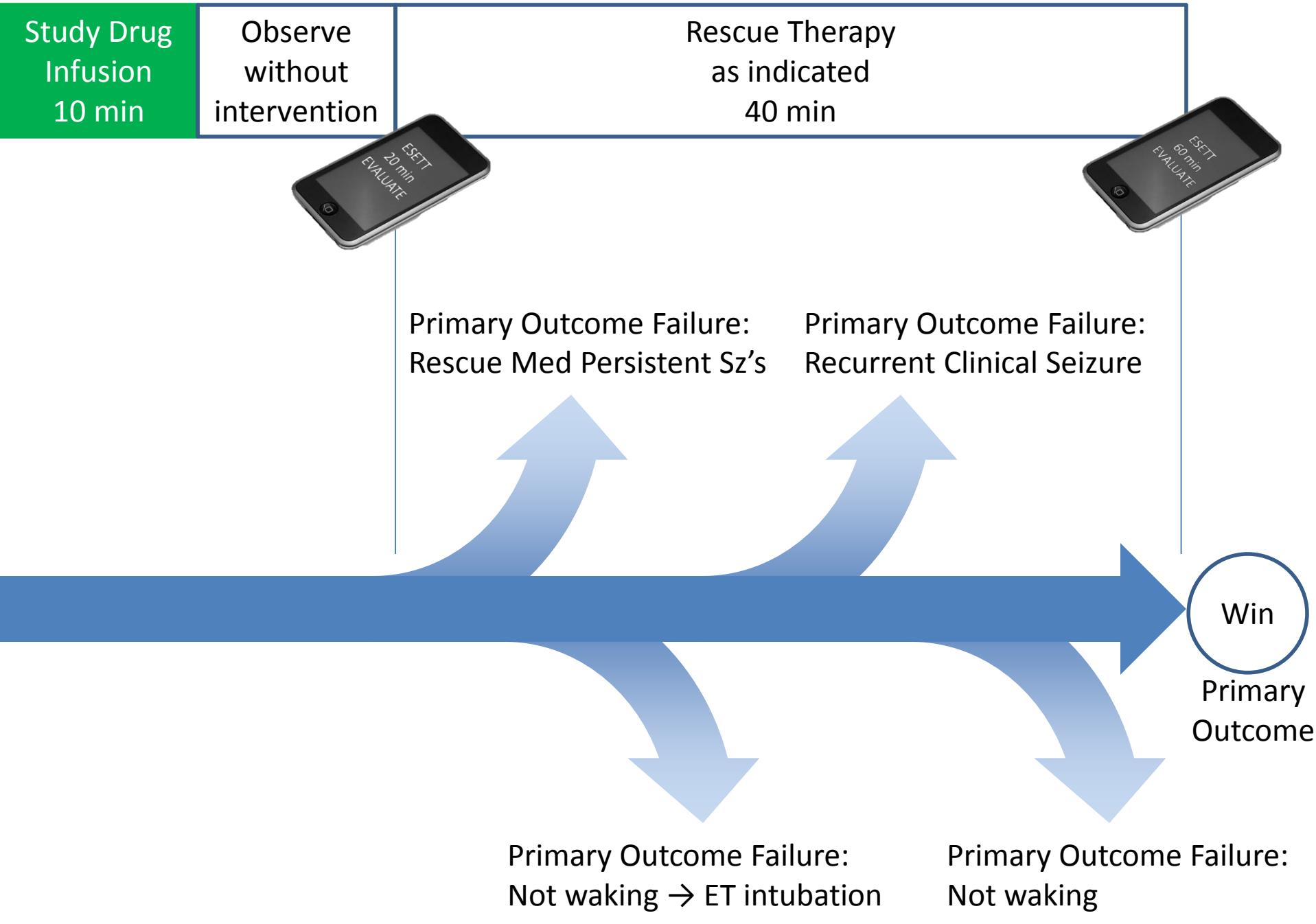
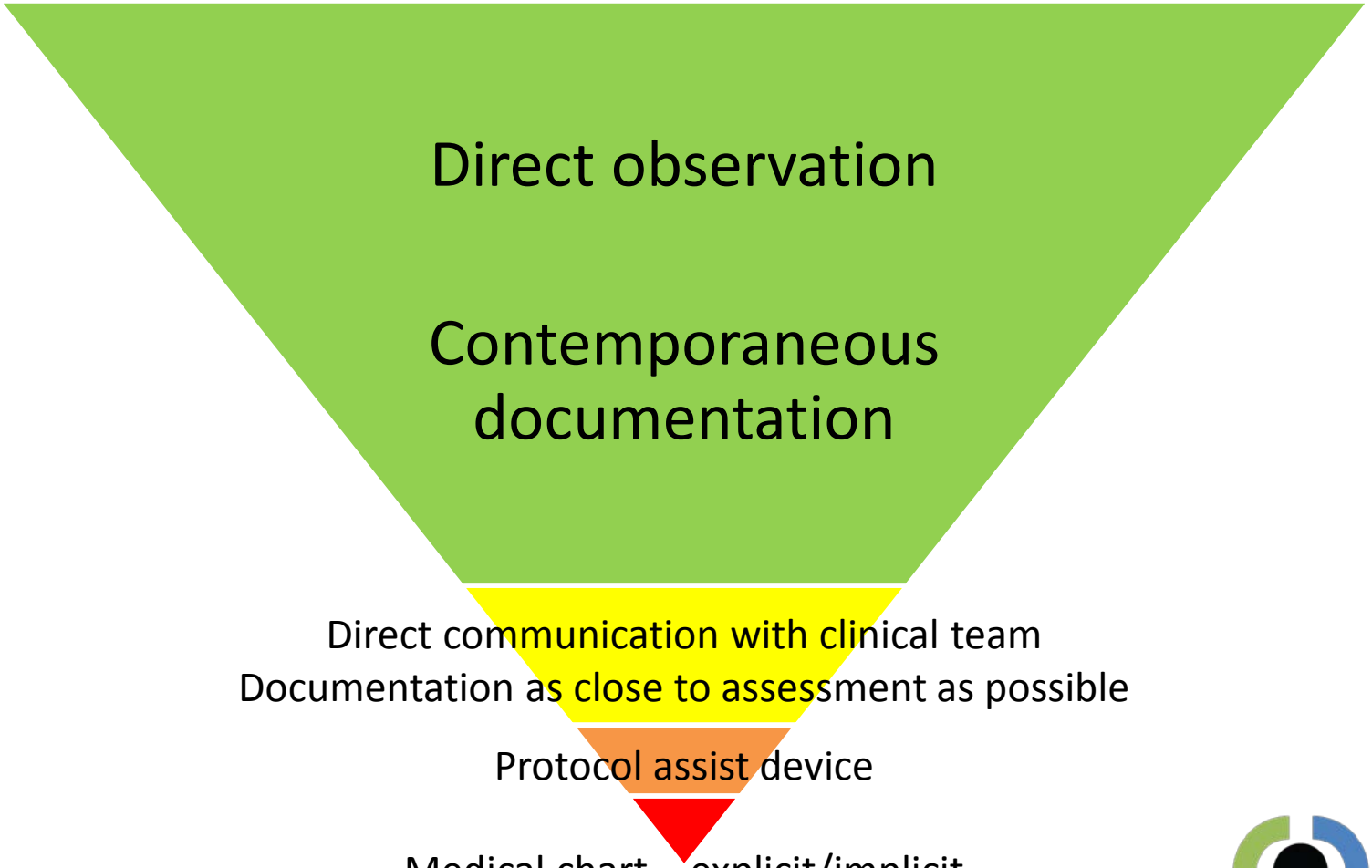

Study Drug Infusion 10 min
Observe without intervention
Rescue Therapy as indicated 40 min
ESETT 20 min EVALUATE
ESETT 60 min EVALUATE
Primary Outcome Failure: Rescue Med Persistent Sz's
Primary Outcome Failure: Recurrent Clinical Seizure
Win
Primary Outcome
Primary Outcome Failure: Not waking → ET intubation
Primary Outcome Failure: Not waking

# Source of Truth

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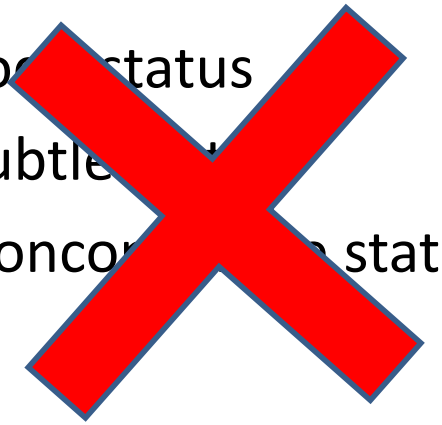
# Clinically Apparent Seizures

- Fo[illegible]status
- Subtle[illegible]
- Noncon[illegible] status



Yes, but usually the question is moot…..

Did they get treated?

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# Additional anti-seizure medication

- Including all oth
- Regardless o
- Rapid sequ
- Most sed
- Give routi in.
- Avoid gratu
- Avoid precipit tubation

carbamazepine, clobazam, dexmedetomidine, diazepam, ethosuximide, etomidate, ezogabine, felbamate fosphenytoin, gabapentin, ketamine, lacosamide, lamotrigine, levetiracetam, midazolam, methohexital, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, propofol, pregabalin, primidone, rufinamide, thiopental, tiagabine, topiramate, valproic acid or valproate, vigabatrin, zonisamide

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# Endotracheal Intubation

- Always as clinically indicated
- But … reinforce best practices
- DO intubate for 3rd line rescue
- DO intubate for underlying reasons (e.g. ICH)
- DO intubate for respiratory failure
- DO intubate for lack of airway
- NOT usually for postictal unresponsiveness
- NOT without seeing if 2nd line agent works

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# Improving Responsiveness

- Responsiveness compared to enrollment
  - Purposeful response to pain?
  - Following commands?
  - Verbalization?

- RASS as a tool

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# Improving Responsiveness

| Score | Term | Description |
|---|---|---|
| **+4** | Combative | Overtly combative, violent, immediate danger to staff |
| **+3** | Very agitated | Pulls or removes tube(s) or catheter(s); aggressive |
| **+2** | Agitated | Frequent non-purposeful movement, fights ventilator |
| **+1** | Restless | Anxious but movements not aggressive vigorous |
| **0** | | Alert and calm |
| **-1** | Drowsy | Not fully alert, but has >10 seconds of awakening to voice |
| **-2** | Light sedation | Briefly awakens with eye contact to voice (<10 seconds) |
| **-3** | Mod. sedation | Movement or eye opening to voice (but no eye contact) |
| **-4** | Deep sedation | No response to voice, but movement or eye opening to physical stimulation |
| **-5** | Unarousable | No response to voice or physical stimulation |

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# Life-threatening hypotension

- Two consecutive low readings 10 min. apart

**And**

- Still low 10 min after ↓ infusion rate + fluids

- Low is
  - SBP < 90 mmHg in adults and kids ≥ 13
  - SBP < 80 mmHg in kids 7 to 12
  - SBP < 70 mmHg in kids younger than 7

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# Life-threatening cardiac arrhythmia

- Persistent arrhythmia despite ↓ infusion rate
- And
- Requires:
  - Chest compressions
  - Pacing
  - Defibrillation
  - Antiarrhythmic agent or procedure

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# Outcome CRF's

- Treatment Effect (Form03)
- Secondary Outcomes (Form04)
- 18 items total (and 11 are conditional)

- Let's practice filling it out.

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You get a text message that a study box was activated. En route, you call to let the clinical team know you are on your way. They have no questions for you and are too busy to talk right now. You arrive and the protocol assist device says it has been 40 minutes since the start of study drug infusion. The patient is not convulsing. The nurse says that she stopped convulsing during the infusion.

You say "Great job, guys. How is it going?

Terrific, this is really easy to do.

Did you happen to do an assessment when the device beeped at 20 min?

Huh?

You said that she stopped seizing during the infusion, but was she not convulsing or waking up 20 minutes after the start of infusion?

Well, I don't think we assessed her right at 20 minutes, but I think she stopped convulsing before that, and she been waking up slowly

Ok, thanks. Can I look at the MAR so far for this visit?

Yes. Here. Nothing since the study drug started.

At 60 min you assess her with the clinical team. She does not follow commands, pushes you away and slurs "leave me alone" to stimuli without looking at you, then returns to sleep. There are no convulsions.

**Form 03: Treatment Effect** (version 1)



| Assessment at 20 minutes | | | |
|---|---|---|---|
| Q1 | Was the 20 minute assessment for seizures/ responsiveness done? | | ○ No ○ Yes ○ Unknown |
| Q2 | *If Q1 = 'Yes'* | Date/time of 20 minute assessment: | __ __ - __ __ __ - __ __ __ __ (dd-mmm-yyyy) / __ __ : __ __ (hh:mm) ○ AM ○ PM |
| Q3 | *If Q1 = 'Yes'* | Were there clinically apparent seizures at 20 minutes after the start of the study drug infusion? | ○ No ○ Yes ○ Unknown |
| Q4 | *If Q1 = 'Yes'* | Was responsiveness to verbal commands or noxious stimuli improved at 20 minutes after the start of study drug infusion compared to responsiveness at the time the study drug infusion began? | ○ No ○ Yes ○ Unknown |

# Was the 20 minute assessment for seizures/responsiveness done?

A. Yes
B. No (correct)

## Form 03: Treatment Effect (version 1)

| Assessment at 20 minutes | | | |
|---|---|---|---|
| Q1 | Was the 20 minute assessment for seizures/ responsiveness done? | | ○ No ○ Yes ○ Unknown |
| Q2 | *If Q1 = 'Yes'* | Date/time of 20 minute assessment: | __ __ - __ __ __ - __ __ __ __ / __ __ : __ __ (dd-mmm-yyyy / hh:mm) ○ AM ○ PM |
| Q3 | *If Q1 = 'Yes'* | Were there clinically apparent seizures at 20 minutes after the start of the study drug infusion? | ○ No ○ Yes ○ Unknown |
| Q4 | *If Q1 = 'Yes'* | Was responsiveness to verbal commands or noxious stimuli improved at 20 minutes after the start of study drug infusion compared to responsiveness at the time the study drug infusion began? | ○ No ○ Yes ○ Unknown |

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Assessment at 60 minutes **(Primary Outcome)**

| | | | |
|---|---|---|---|
| Q5 | Was the 60 minute assessment for seizures/ responsiveness done? | | ○ No ○ Yes ○ Unknown |
| Q6 | *If Q5 = 'Yes'* | Date/time of 60 minute assessment: | __ __-__ __ __-__ __ __ __ / __ __:__ __ ○ AM ○ PM<br>dd-mmm-yyyy hh:mm<br>0 2 d e c 2 0 1 5 1 1 1 2 |
| Q7 | *If Q5 = 'Yes'* | Were there clinically apparent seizures at 60 minutes after the start of the study drug infusion? | ○ No ○ Yes ○ Unknown |
| Q8 | *If Q5 = 'Yes'* | Was responsiveness to verbal commands or noxious stimuli improved at 60 minutes after the start of study drug infusion compared to responsiveness at the time the study drug infusion began? | ○ No ○ Yes ○ Unknown |

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**Form 03: Treatment Effect** (version 1)



| | | | |
|---|---|---|---|
| Q9 | *If Q5 = 'Yes'* | Richmond Agitation Sedation Scale (RASS) at 60 minute assessment: | ○ +4 Combative (Overtly combative, violent, immediate danger to staff)<br>○ +3 Very agitated (Pulls or removes tube(s) or catheter(s); aggressive)<br>○ +2 Agitated (Frequent non-purposeful movement, fights ventilator)<br>○ +1 Restless (Anxious but movements not aggressive vigorous)<br>○ 0 Alert and calm<br>○ -1 Drowsy (Not fully alert, but has sustained awakening (eye-opening/ eye contact) to voice (>10 seconds))<br>○ -2 Light sedation (Briefly awakens with eye contact to voice (<10 seconds))<br>○ -3 Moderate sedation (Movement or eye opening to voice (but no eye contact))<br>● -4 Deep sedation (No response to voice, but movement or eye opening to physical stimulation)<br>○ -5 Unarousable (No response to voice or physical stimulation) |

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| | | | | | |
|---|---|---|---|---|---|
| Q10 | Aside from the study drug, were any other anti-seizure medications administered within 60 minutes after the study drug infusion began?<br><br>(see MOP for a list of anti-seizure medications) | | ● No | ○ Yes | ○ Unknown |
| | *If Q10 = 'Yes'* | A.<br>Date/time other anti-seizure medications administered within 60 minutes after study drug infusion | B.<br>Medication name | C.<br>Dose | D.<br>Dose Units |
| Q11-1 | *If Q10 = 'Yes'* | __ __ - __ __ __ - __ __ __ __<br>dd-mmm-yyyy<br>__ __ : __ __ ○ AM ○ PM | | | |
| Q11-2 | *If Q10 = 'Yes'* | __ __ - __ __ __ - __ __ __ __<br>dd-mmm-yyyy<br>__ __ : __ __ ○ AM ○ PM | | | |

| | | | |
|---|---|---|---|
| Q12 | Was this form completed at the subject's bedside at the time of assessment? | | ○ No ○ Yes |
| Q13 | *If Q12 = 'No'* | How was the information for questions 7, 8, and 10 on this form determined?<br><br>Check all that apply | ☐ Discussion with the treating team within 3 hours of the 60 minute assessment<br>☐ Discussion with the treating team more than 3 hours after the 60 minute assessment<br>☐ Medical Record |

General Comments:

Name of person who collected data:
If this worksheet is a source document, sign/date here:

You look over the ED chart and notice a couple of low blood pressure readings, 85/44 and then 83/35 but the sequence of events is unclear, so you ask the nurse.

Can you tell me about these low BP's?

Yeah, those happened at the end of the infusion, but it has been better since then.

Were there any other BP readings that have not been documented yet?

Nope

Any heart rhythm problems?

There was some bradycardia around the same time, but it got better after the infusion ended too.

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# Did the subject experience life-threatening hypotension?

A. Yes
B. No (correct)

If 'yes' for any question below, complete a corresponding AE form.

Life-threatening hypotension is defined as systolic blood pressure remaining below the age-specified thresholds on two consecutive readings at least 10 minutes apart and remaining below the age-specified thresholds for more than 10 minutes after reduction of the rate of study drug infusion rate (or its termination) and a fluid challenge. The "age-specified thresholds" for systolic blood pressure are 90 mmHg in adults and children 13 years and older, 80 mmHg in children 7 to 12 years old, and 70 mmHg in children through 6 years of age.

| | | | | |
|---|---|---|---|---|
| Q1 | Did the subject experience life-threatening hypotension within 60 minutes of the start of study drug infusion? | ● No | ○ Yes | ○ Unknown |
| Q2 | Did the subject experience life-threatening cardiac arrhythmia within 60 minutes of the start of study drug infusion? | ● No | ○ Yes | ○ Unknown |

| | | | | |
|---|---|---|---|---|
| Q3 | Was endotracheal intubation performed or attempted within 60 minutes of the start of study drug infusion? | ● No | ○ Yes | ○ Unknown |
| Q4 | Did the subject experience acute seizure recurrence between 60 minutes and 12 hours after the start of study drug infusion? | ● No | ○ Yes | ○ Unknown |
| Q5 | Did the subject experience acute anaphylaxis within 6 hours of the start of study drug infusion? | ● No | ○ Yes | ○ Unknown |
| General Comments: | | | | |
| Name of person who collected data:<br>If this worksheet is a source document, sign/date here: | | | | |

A subject stops convulsing after getting study medication and has increasing responsiveness but does not follow commands. A CT scan shows a large SAH and is intubated for that indication.

**Does this patient meet or fail the primary outcome?**

A. Meet
B. Fail (correct)

Same case. A subject stops convulsing after getting study medication and has increasing responsiveness but does not follow commands. A CT scan shows a large SAH and is intubated for that indication. **Should the study team ask for the intubation to be delayed until after 60 minutes?**

A. Yes, because this would make the outcome more informative
B. No, not unless the intubation is elective and delay is clinically appropriate (correct)

A subject develops bradycardia to 50 bpm during study drug infusion. The infusion rate is reduced, the rate recovers, no other interventions. **Is this a life-threatening cardiac arrhythmia on Form04?**

A. Yes
B. No (correct)

Same situation. A subject develops bradycardia to 50 bpm during study drug infusion. The infusion rate is reduced, the rate recovers, no other interventions. **Is this an adverse event?**

A. Yes (correct)
B. No

# Additional Vignettes

A 20 month old. male began seizing at home earlier in the day. Seizure had focal onset and generalized. There is a prior history of febrile status at age 18 months and child was felt hot to the touch. Parents gave Diastat 7.5 mg rectally at 5 minutes. No additional meds given in ambulance. He arrives at the ED actively convulsing 25 minutes after seizure onset.

A. He is eligible because continues to have seizures despite diazepam and should be randomized.
B. He is not eligible because he only received rectal diazepam and needs to receive a dose of IV or IM benzodiazepenes before being eligible
C. He is not eligible because his benzodiazepines were too long ago
D. He is not eligible because he is too young
E. B & D (correct)

A 29 y.o. woman is found convulsing outside the back door of a fertility clinic. Paramedics attend and give 10mg IM midazolam following which she is still and sedated for 15mins, but the time they arrive in the ED she is convulsing again and a 2nd dose of midazolam is given

A. She is not eligible because she may be pregnant.
B. She is not eligible because the onset time is unknown
C. She is not eligible until 5 minutes after the 2nd dose (correct)
D. She is eligible and should be randomized
E. She is not eligible until she has been scanned and an acute cerebral event excluded

An 83y man with known Alzheimer's disease collapses in his residential home with a witnessed first generalized convulsive seizure which was terminated after 15mins by 10mg PR Diazepam. He is brought to the ED and 20mins later hasn't regained consciousness. O/E his GCS is 6/15 and he has rhythmic nystagmoid eye movements.

A. He is eligible now and should be randomized.
B. He is not eligible due to his Alzheimer's disease
C. He will only become eligible if he has a further overt convulsive seizure within the next 10 minutes (correct)
D. He is not eligible as his seizure has terminated
E. He is not eligible as he will likely need intubation/sedation for urgent brain imaging

A 28 y.o. woman with cognitive impairment and frequent GTC seizures was found convulsing by her parents and given 10 mg rectal diazepam. Seizure activity continued for another 5 minutes and EMS arrived 10 minutes later and gave 10 mg IV diazepam. She arrives in the ED 5 minutes later and has a subtle whole body jerk every 3 seconds.

A. She is eligible because she continues to have seizures despite diazepam and should be randomized. (correct)
B. She is not eligible because she has received enough benzodiazepines yet.
C. She is not eligible because seizure activity is too subtle.
D. She is not eligible because she has been seizing too long.

A 54 y.o. previously healthy man had a GTC at 10:50 a.m. and was seen in the ED and discharged. He had a second GTC at 18:07. He had a third en-route to the ED. He is unresponsive in the ED with low amplitude, focal motor activity unresponsive to 5 mg IV midazolam given on arrival and again 25 minutes prior.

A. He is eligible because he continues to have seizures despite midazolam and should be randomized. (correct)
B. He is not eligible because the last dose of benzodiazepines was too long ago.
C. He is not eligible because seizure activity is limited to the face.
D. He is not eligible because he has been seizing too long.