Virtual

# ESETT Investigator Meeting

October 4, 2017

October 24, 2017

# Agenda

- Study Update
  - Enrollment
  - Protocol-assist device usage
- Protocol Adherence
- PK/PD Sub-study Training
- Ongoing Training of Clinical Staff
  - Peer-to-peer Best Practices
  - 5 minute Educational Module preview
- Adverse Event Reporting

# Enrollment

Total enrolled subjects: **383**

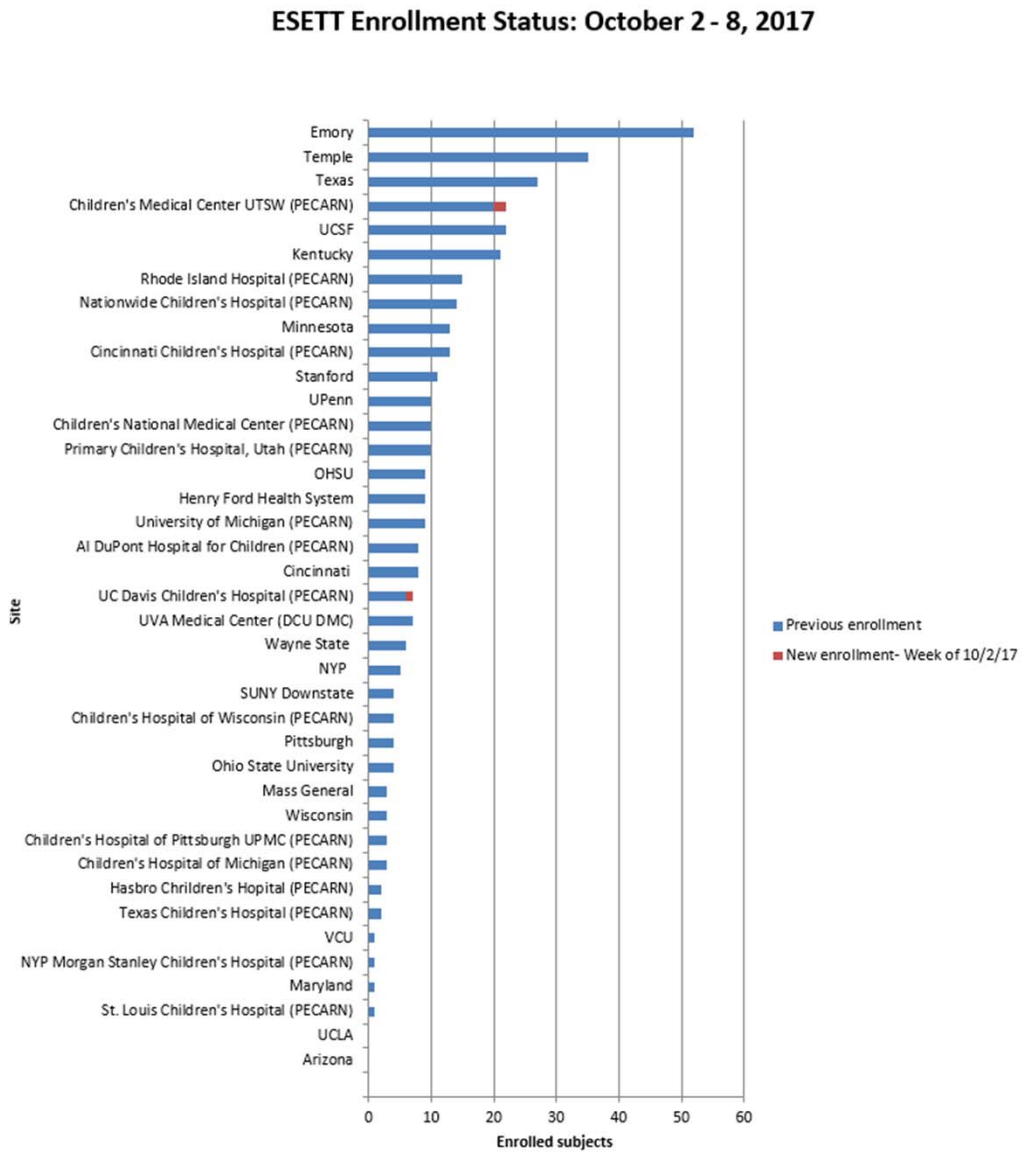
Child (2-17): **146**

Younger Adult (18-65): **181**

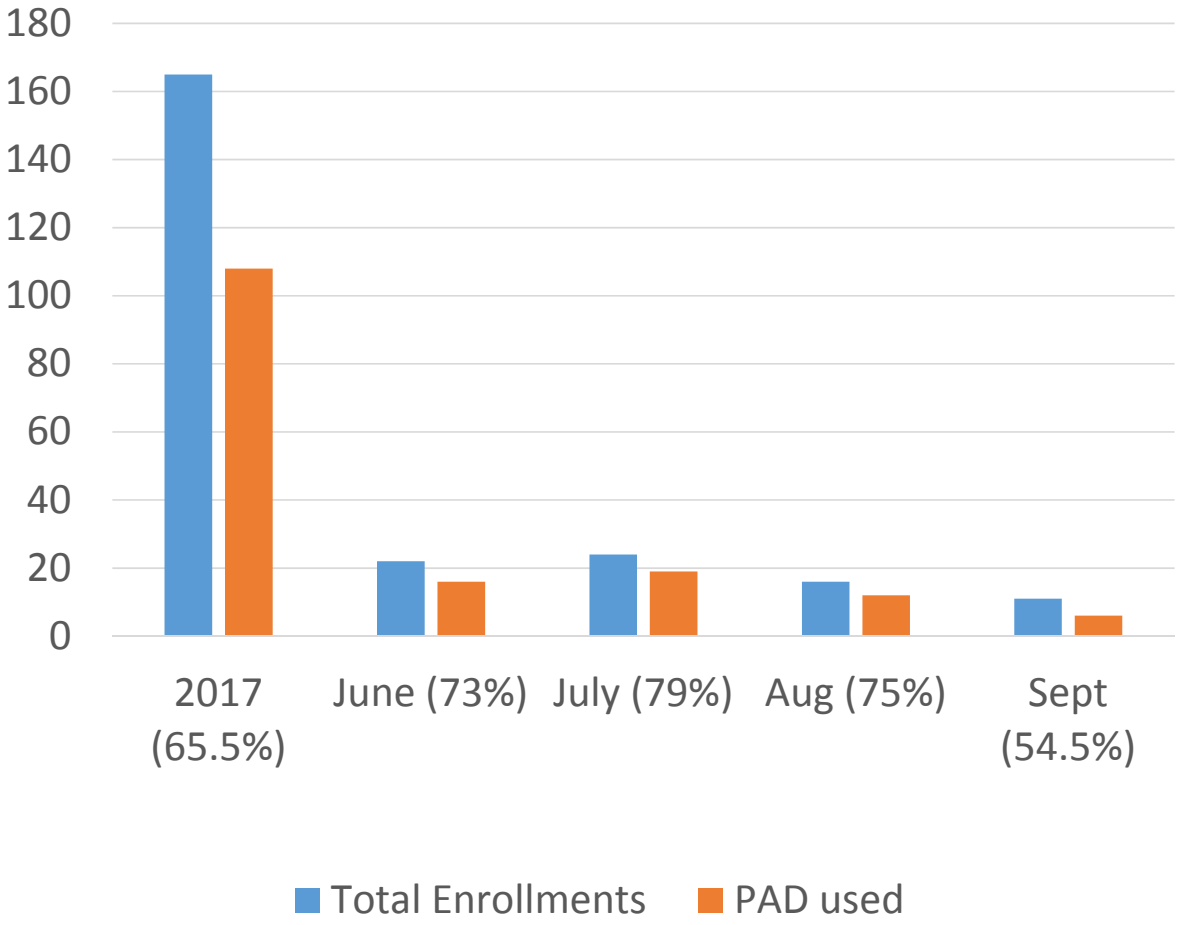
Older Adult (66 or older): **56**

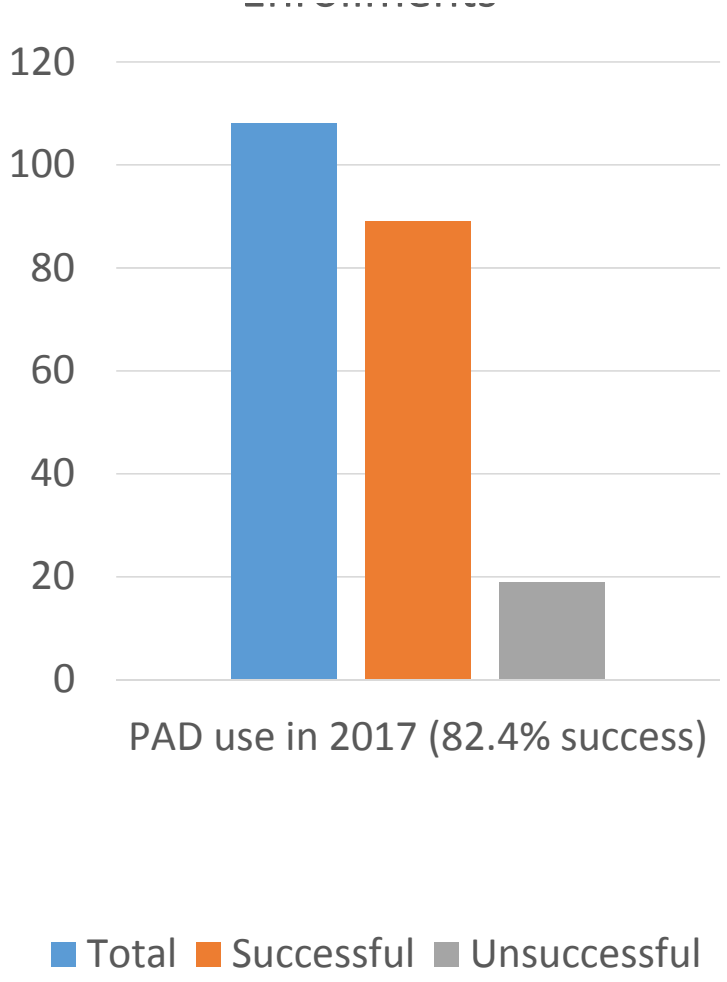
Active Sites (NETT and PECARN): **63**

Recent enrollers: Children's Medical Center, UTSW (3!), University of Utah, San Francisco General Hospital, UC Davis

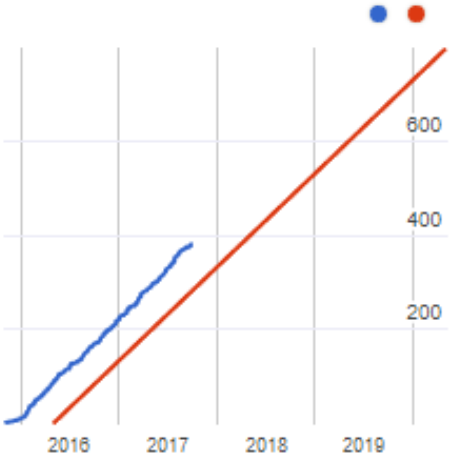


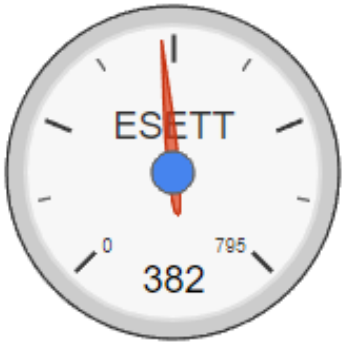
# Protocol Assist Device Usage

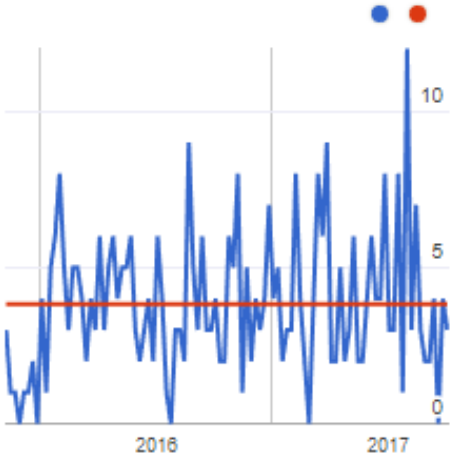


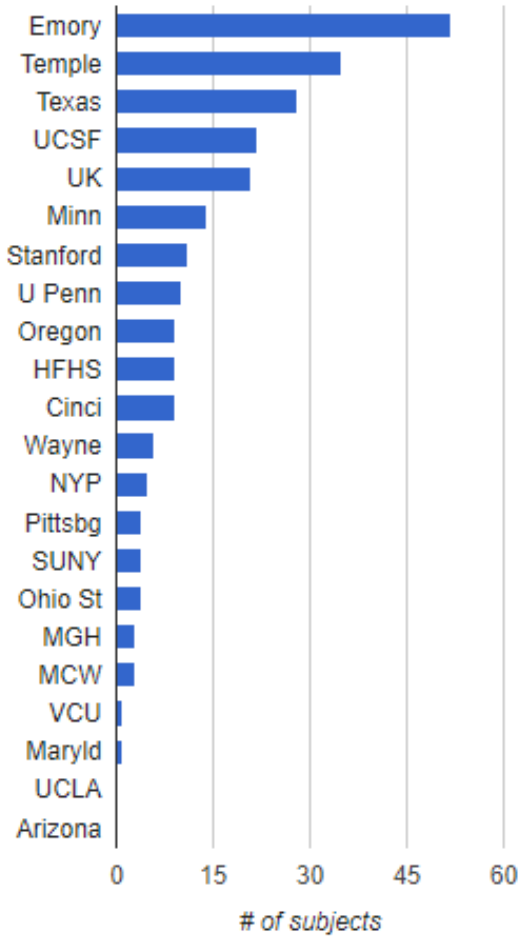



# Progress




NIH Funding year 3

# Progress report

Children 38%
Young adults 47%
Older adults 15%

Total Sites: 63
At least 1 subject enrolled at 53 sites

Drugs: Lot 2 in use; a back up lot ready.
Phenomenology core adjudicated 331 subjects.

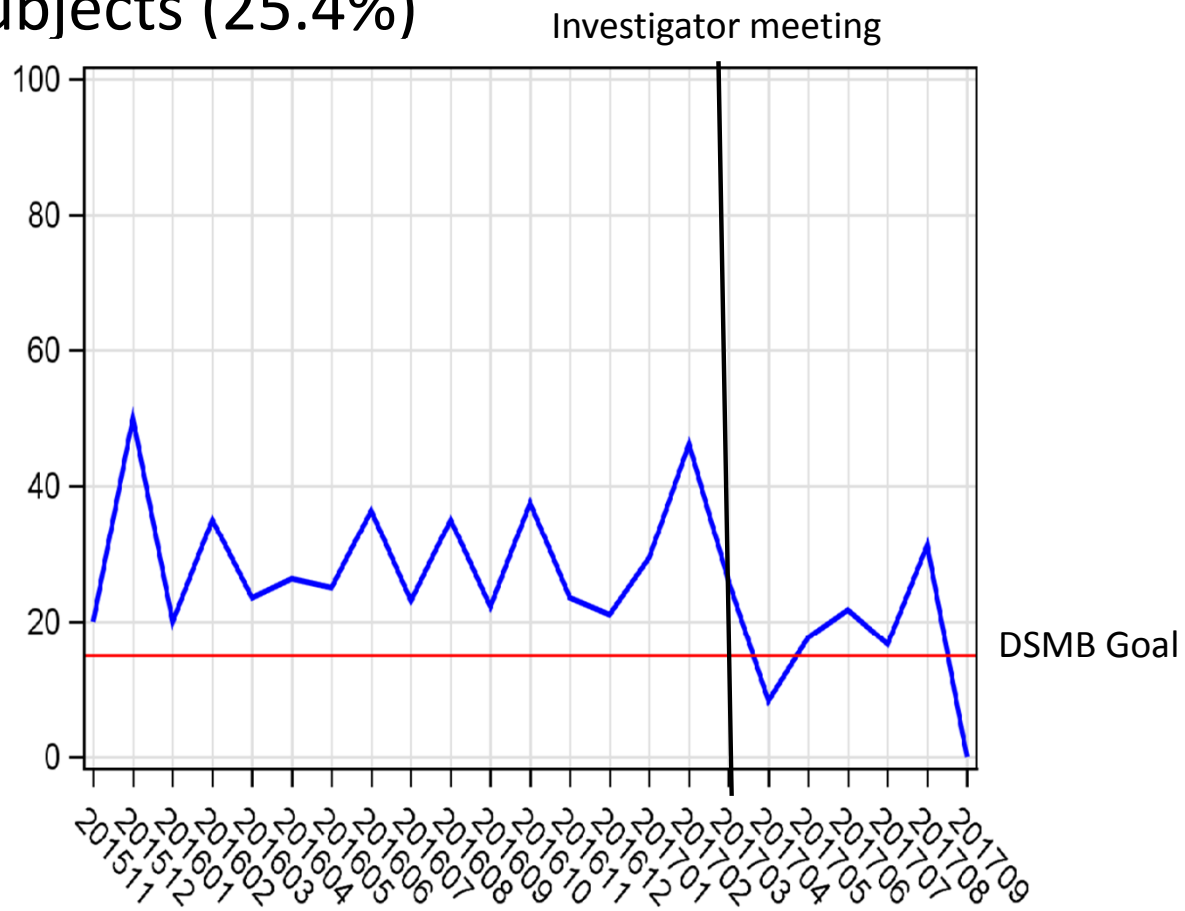
Last DSMB meeting August 4th
FDA report sent August 2018

# Protocol Adherence

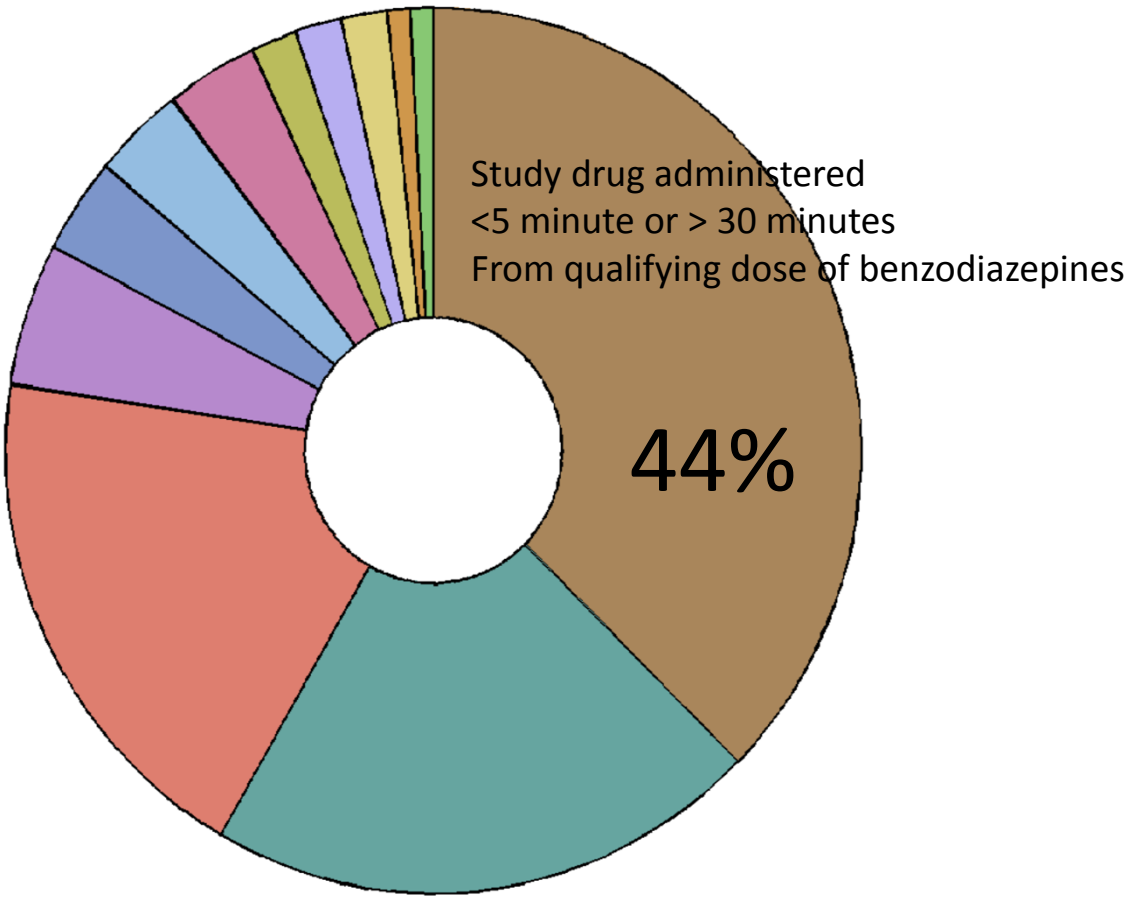
October 2017

# Eligibility Deviations

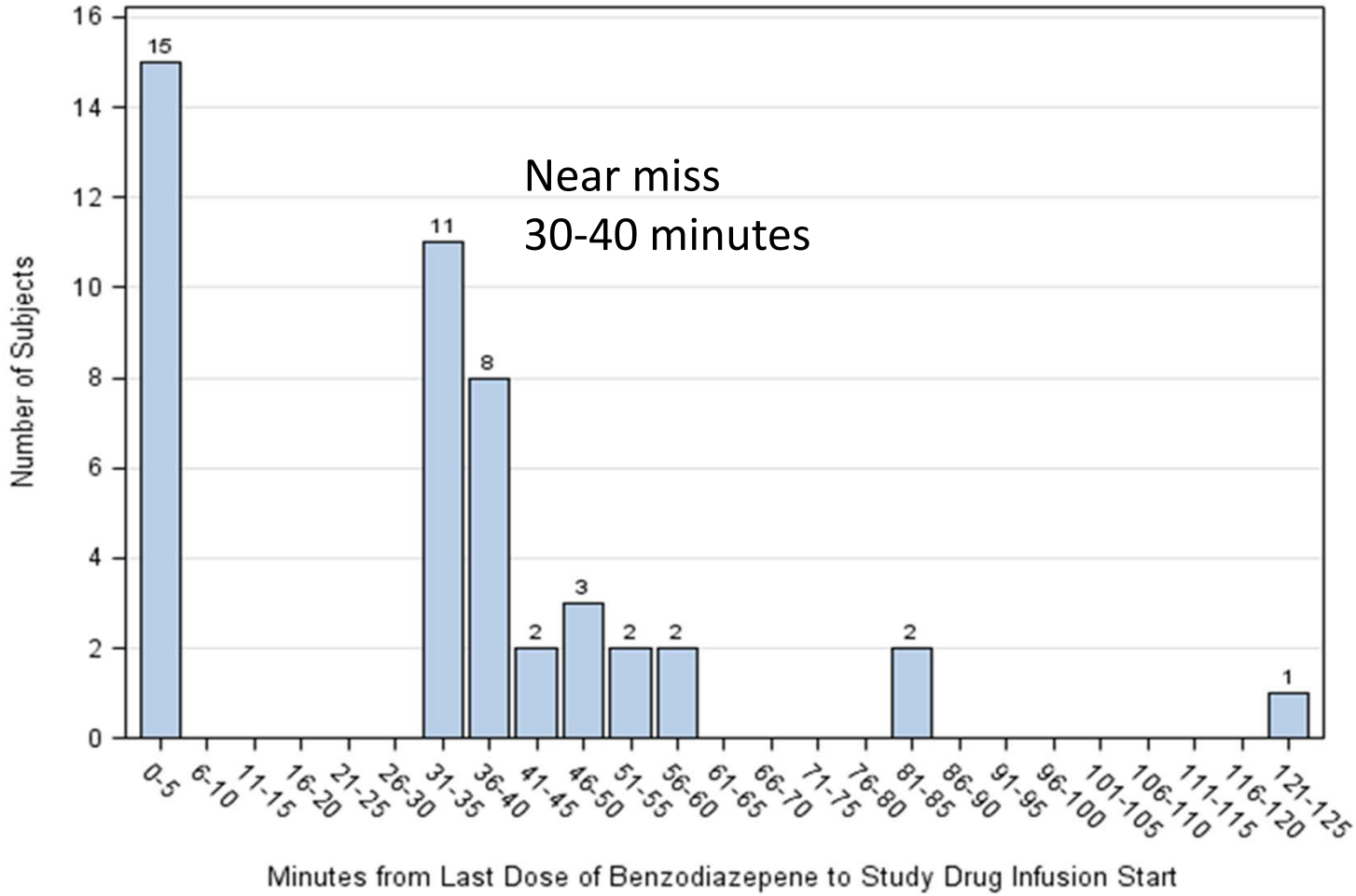
97 subjects (25.4%)



# Nature of deviations

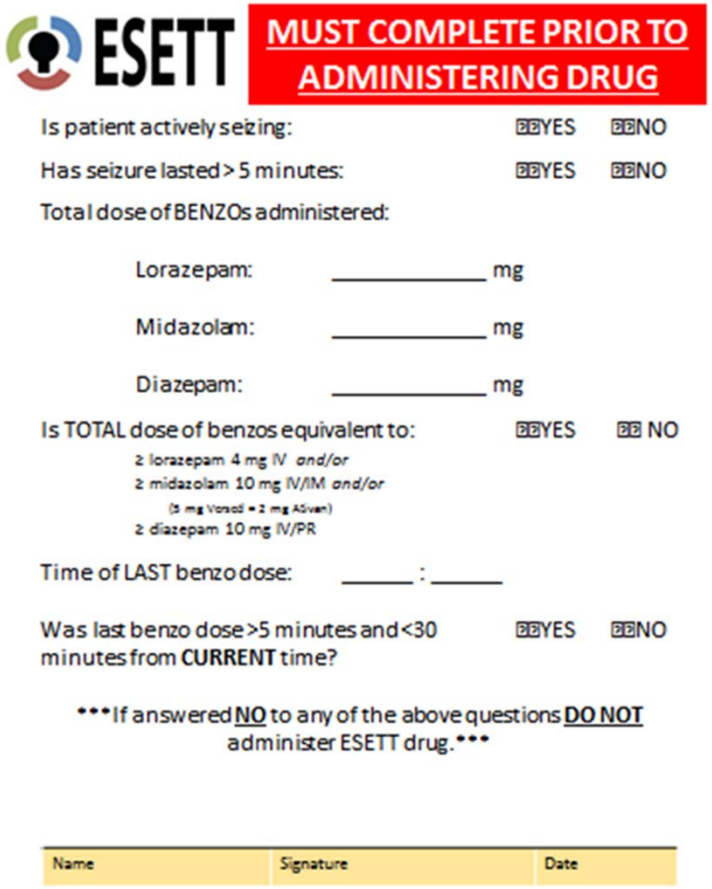


# Timing of benzodiazepines



# Preventing near misses

- Modified ESETT app on Protocol assist device.
- Cards available to fix on top study box.
- Increased awareness of the protocol



ESETT

**MUST COMPLETE PRIOR TO ADMINISTERING DRUG**

Is patient actively seizing: ☐YES ☐NO

Has seizure lasted > 5 minutes: ☐YES ☐NO

Total dose of BENZOs administered:

Lorazepam: _____ mg

Midazolam: _____ mg

Diazepam: _____ mg

Is TOTAL dose of benzos equivalent to: ☐YES ☐ NO

≥ lorazepam 4 mg IV *and/or*
≥ midazolam 10 mg IV/IM *and/or*
(5 mg Versed + 2 mg Ativan)
≥ diazepam 10 mg IV/PR

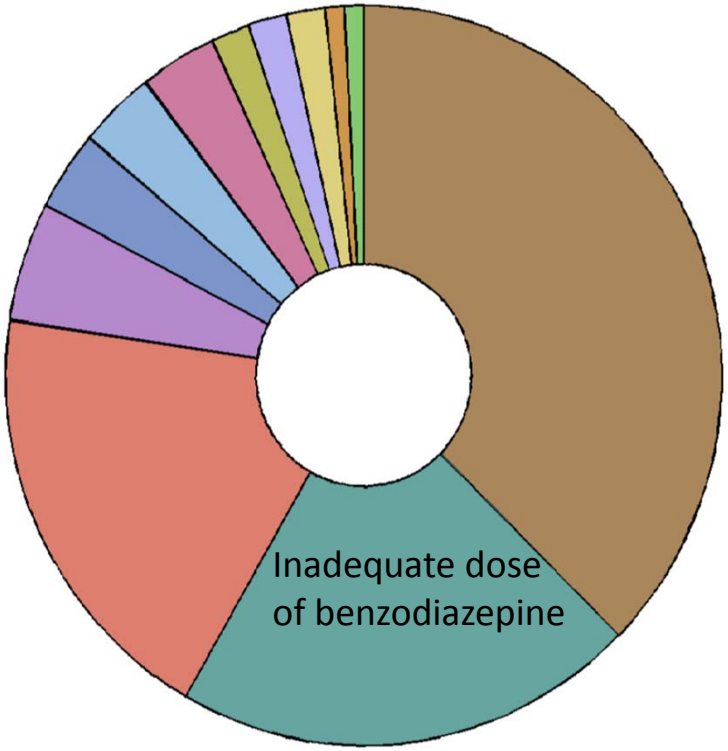
Time of LAST benzo dose: _____ : _____

Was last benzo dose >5 minutes and <30 minutes from **CURRENT** time? ☐YES ☐NO

***If answered **NO** to any of the above questions **DO NOT** administer ESETT drug.***

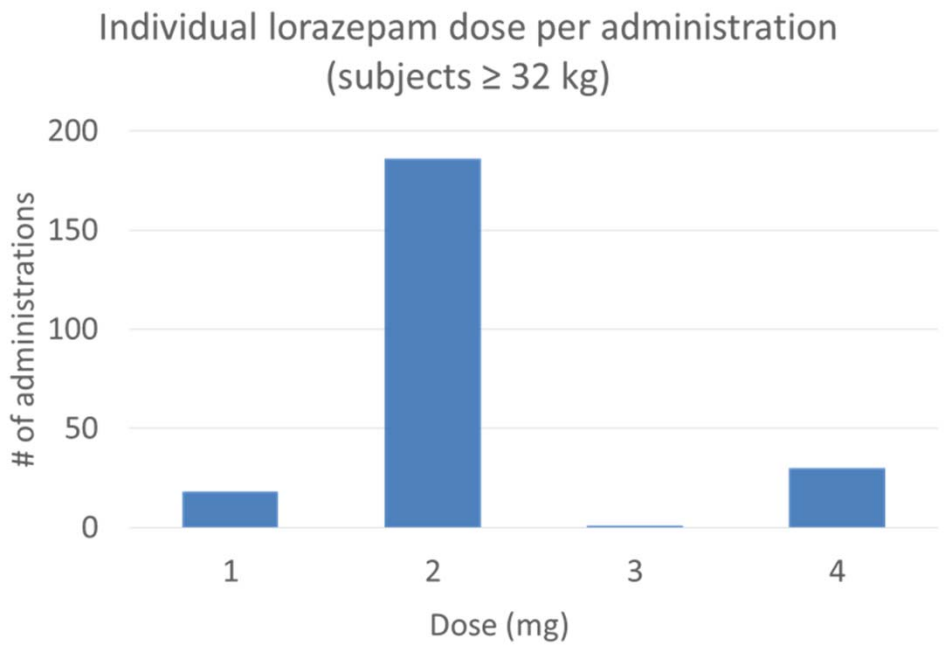
| Name | Signature | Date |
|---|---|---|

# Causes of eligibility deviations



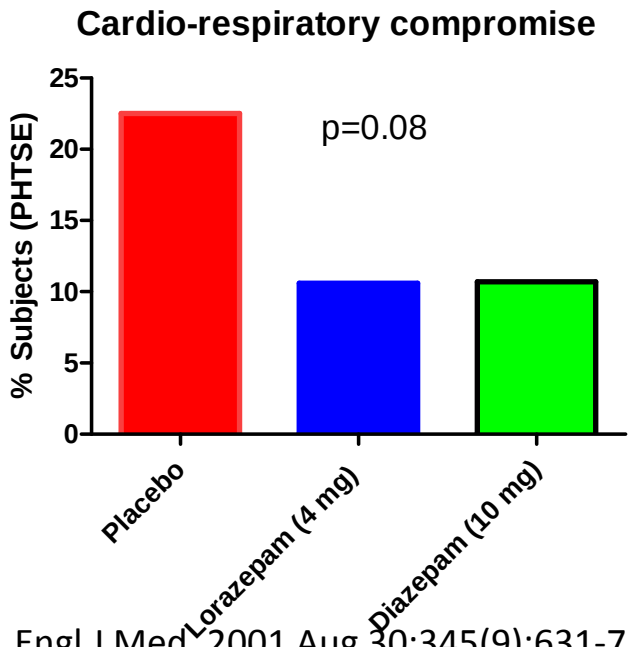
# Under-dosing Benzodiazepine: a common practice

- Review of 207 patients enrolled in ESETT
- In 207 subjects, there were 511 benzodiazepine administrations (312 lorazepam, 159 midazolam, 40 diazepam).



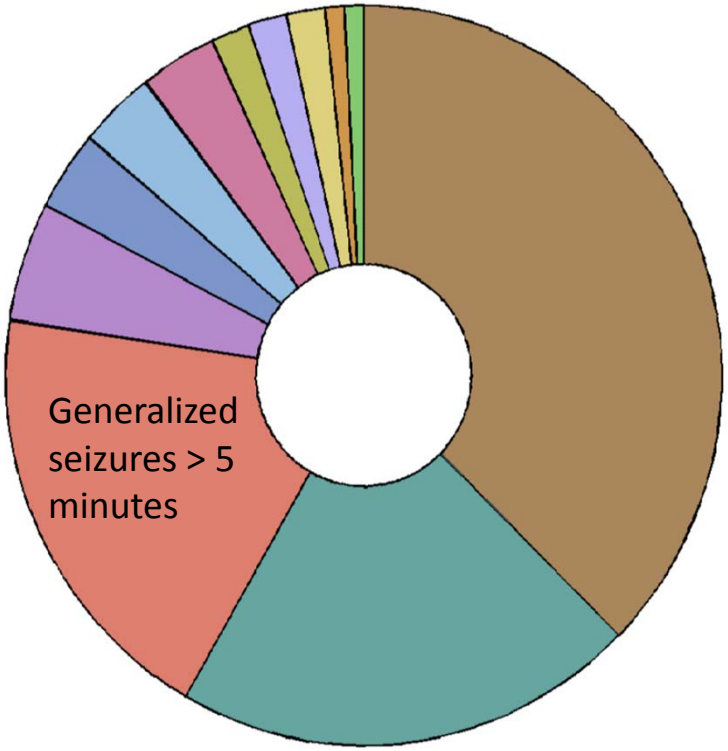
# Small dose safer or more dangerous?

- Do benzos cause cardio respiratory compromise?
- However PHTSE trial data suggest that under-treatment is more dangerous.




N Engl J Med. 2001 Aug 30;345(9):631-7.

# Causes of eligibility deviations



# GTCS > 5 minutes

- Psychogenic non epileptic seizures: if the chart has this diagnosis/ you know that they have PNES.
- Focal seizures.

| | |
|---|---|
| Known metabolic disorder | Clinical history* |
| Known liver disease | Clinical history* |
| Known severe renal impairment | Clinical history* |
| Known allergy or other known contraindication to FOS, PHT, LEV, or VPA | Clinical history |
| Hypoglycemia < 50 mg/dL | Finger-stick glucose |
| Hyperglycemia > 400 mg/dL | Finger-stick glucose |
| Cardiac arrest / post-anoxic seizures | History and ECG rhythm strip |

# Emergency unblinding

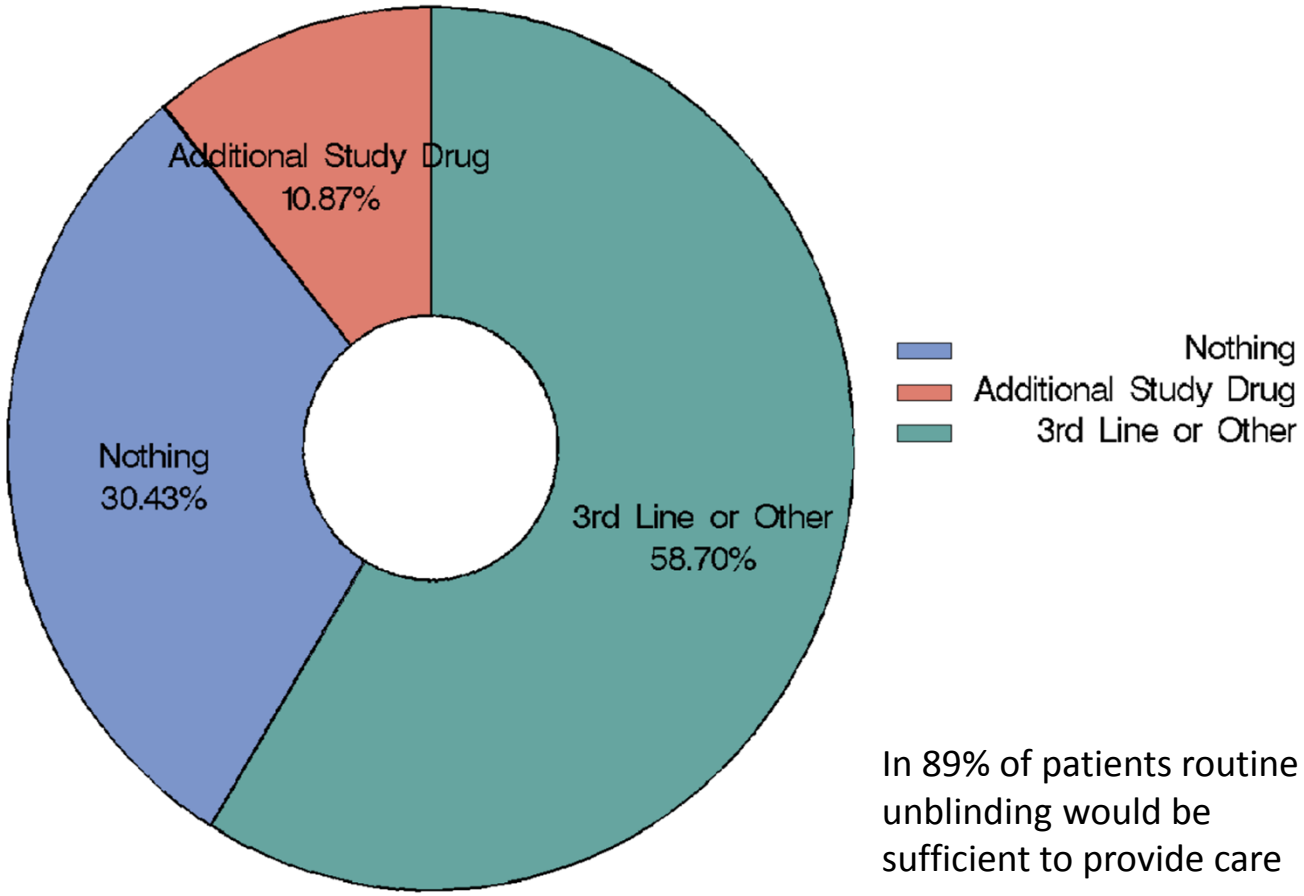
- DSMB recommendation:  to work with sites to minimize unnecessary cases of study drug unblinding.

# Emergency Unblinding

- Emergency unblinding rate is currently 13%. A study drug (second or additional study drug) was used after unblinding in this fraction:

  a) 75%
  b) 37%
  c) 18%
  d) 11%

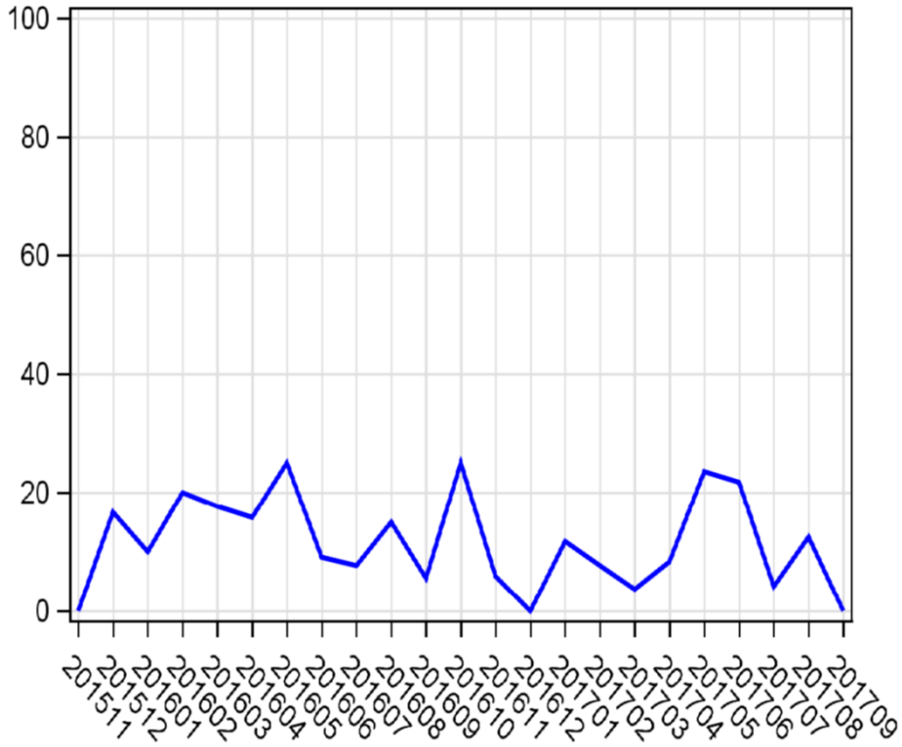
## Treatment After Emergency Unblinding




In 89% of patients routine unblinding would be sufficient to provide care

# Emergency Unblinding

Trial PIs will ask to speak with treating physician discuss the need for emergency unblinding. Would it affect any treatment decisions within the 60 minutes time frame?



# Emergency unblinding

- After any unnecessary emergency unblinding the site PI will be contacted. Site PI will decide on a corrective action plans such as reeducation.

# Thank you!

- Trial continues to enroll patients ahead of schedule.
- It has entered adaptive phase.  Next adaptive re-allocation will occur when 400 subjects have accrued.

# ESETT PHARMACOKINETIC-PHARMACODYNAMIC (PK/PD) STUDY TRAINING

ESETT VIRTUAL INVESTIGATOR MEETING
OCTOBER 4, 2017

Lisa Coles, MS, PhD
Research Assistant Professor
Dept of Experimental and Clinical Pharmacology
University of Minnesota

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# Rationale

- **Substantial variability in drug concentrations occurs following administration of AED loading doses**
- **ESETT protocol uses a mg/kg basis for dosing capped at 75 kg**
- **Variability in early drug concentrations can be high even at the same mg/kg dose**
- **Unknown if drug concentrations correlate with efficacy in management of SE**

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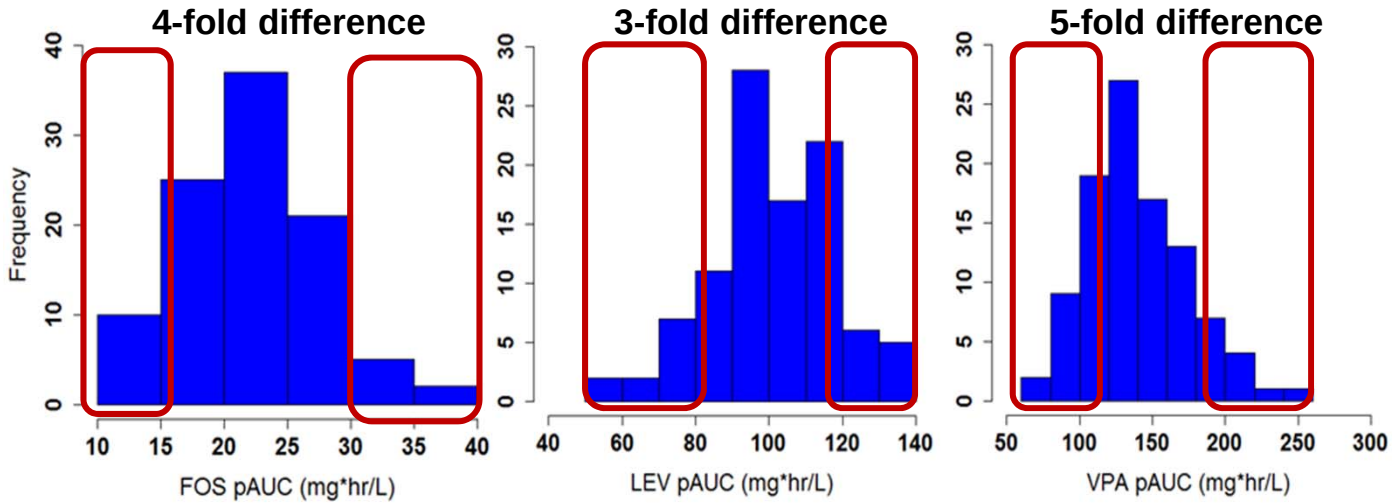
# Simulations Show Wide Variability in Drug Exposure (plasma concentration) Following IV Dosing




**Distributions of cumulative PHT, LEV, and VPA concentrations over 60 min (pAUC) simulated for 100 ESETT patients**

**Does variability in concentrations explain response?**

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# Specific Aim

**Relate drug exposure (concentration or pAUC) with seizure cessation and the key secondary outcomes.**

- ***Hypothesis 1: Patients with higher drug exposures (unbound or total plasma concentrations of FOS, LEV, and VPA) will more likely respond.***
- ***Hypothesis 2: Patients with higher drug exposures will have a higher incidence of serious adverse effects commonly associated with the study drugs.***
- ***Hypothesis 3: The relationship between drug exposure and response will differ by gender, age, weight, and/or BMI.***

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# Study Overview

**Population - Same as ESETT**

**Inclusion Criteria**

- **All subjects randomized under the ESETT protocol.**
- **Able to provide blood sample(s)**

**Overview of Procedures**

- **Collect subject height**
- **Collect two blood samples within specified time ranges**

**Sample and Data Analysis (completed at UofMN)**

- **VPA (total and unbound), PHT (total and unbound) and LEV (total) concentrations measured in plasma**
- **Statistical and pharmacokinetic/pharmacodynamic analyses**

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# Consenting Considerations

- **Blood collection, as part of the ESETT protocol, will occur under exception from informed consent (EFIC).**
- **If patient, parent, or other legally authorized representative (LAR) withdraws consent to continue participation from ESETT, they have also withdrawn from the PK/PD study.**

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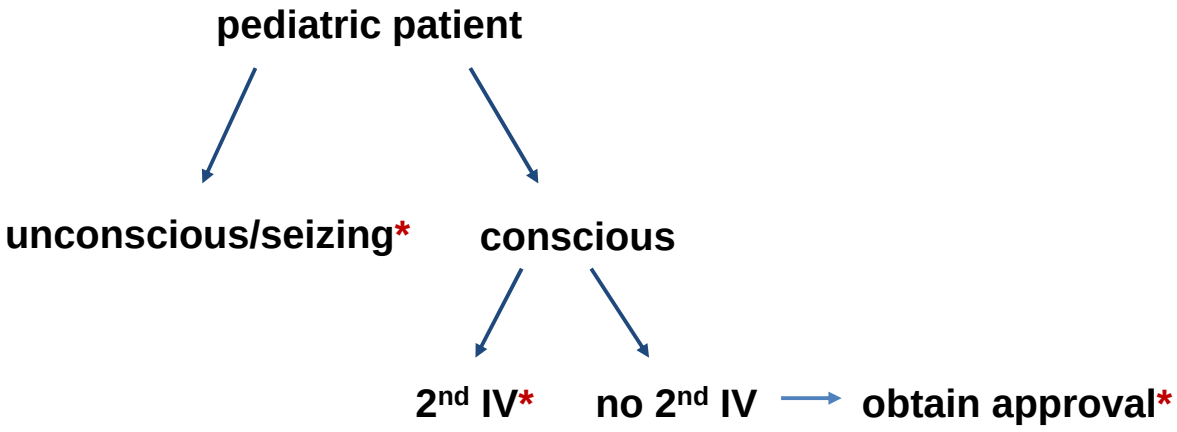
# Consenting Considerations

- **For children who are conscious and do not have a second IV catheter available for blood collection, the parent or LAR should be asked if blood may be drawn by venipuncture for research purposes. If the answer is no, blood should not be collected. Further participation in ESETT should not be affected.**
  - **Even if patient, parent or other LAR informs that study team that he/she does not want blood sample(s) collected, he/she can still participate in ESETT.**




* collect sample

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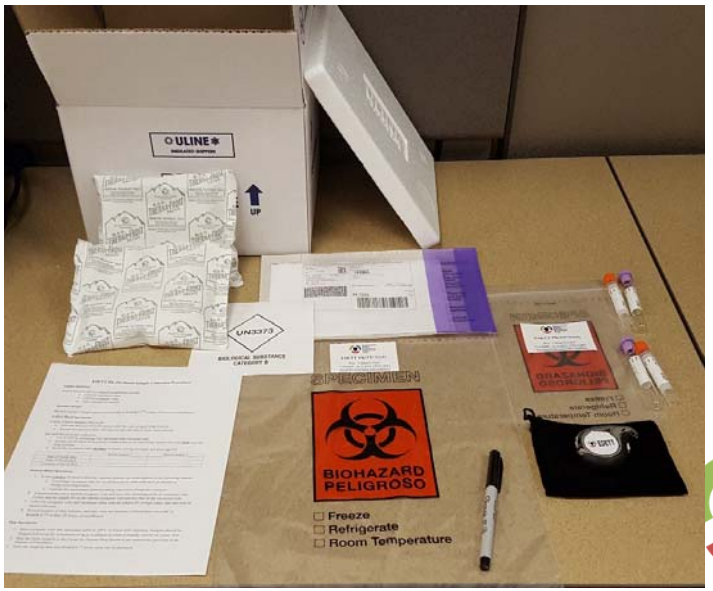
# Materials

- **Supply kits will be provided to research coordinators and will include:**
  - **Labeled 7-mL lavender top vacutainer tubes (2 per subject)**
  - **Labeled 5 mL cryogenic vials (2 per subject)**
  - **Sharpie®**
  - **Tape measure**
  - **Sample collection procedures quick guide**
  - **Copy of PK eCRF**
  - **Biohazard bags**
  - **Absorbent pad**
  - **Shipping materials (cold packs, insulated boxes, biological substance label, and pre-paid FEDEX shipping labels)**

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# Measurement of Height

- **Measure the patient's height (using the official ESETT tape measure) and record in the medical record, eCRF worksheet, or directly in the ESETT PK eCRF.**
- **If height can't be measured, a previously recorded height or estimated height should be recorded.**


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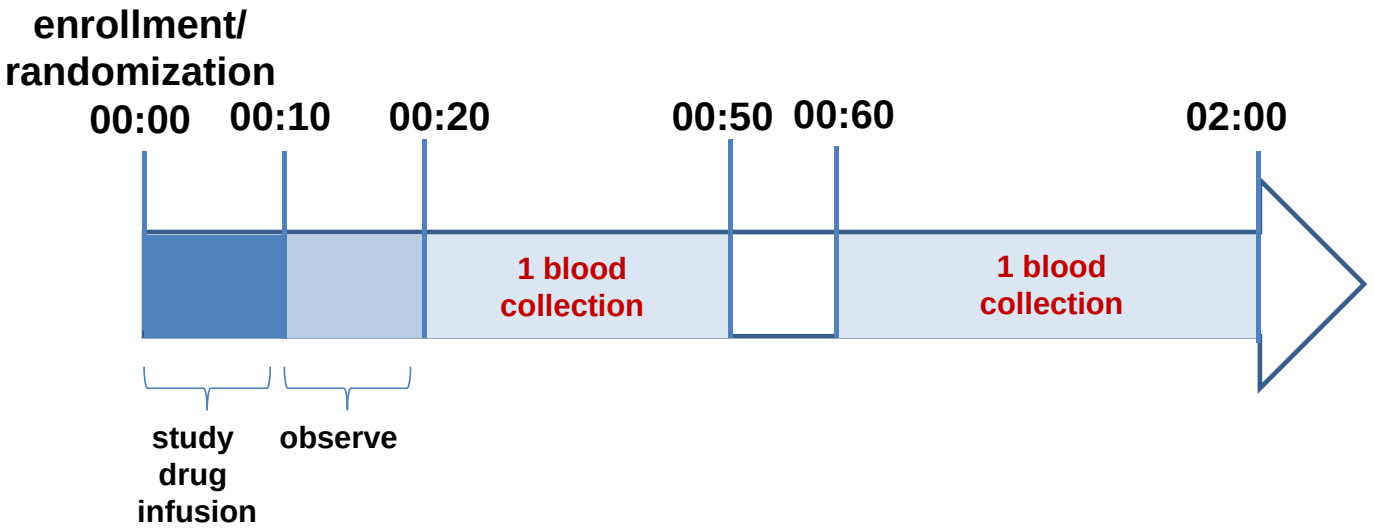
# PK/PD Sample Collection Timetable

- **Collect two blood samples (2.5-3 mL/sample)**
  - **One sample between 20-50 min and a second sample between 60-120 min from the start of drug infusion**

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# Blood Collection Procedures

- To ensure the PK samples are collected correctly mark the infusion site with an 'X' on the bandage.
- For each blood sample (2.5 - 3 mL) use an EDTA-containing vacutainer (lavender top) 7 mL tube.
- Blood can be taken from either direct venipuncture or an indwelling catheter that was NOT used for drug infusion.
- Invert the vacutainer tube approximately 10 times to ensure adequate mixing of blood and anticoagulant.
- Label tube with study drug ID, date, and time of blood collection
- Record the subject and sample IDs, date, time, and whether the PK sample was drawn from the study drug infusion site in the medical record, eCRF worksheet, or directly on the ESETT PK blood collection eCRF.


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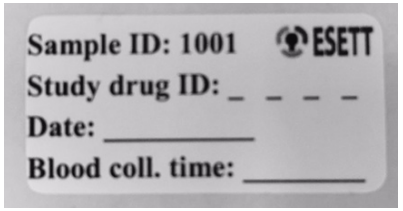
# Blood Sample Processing

- **Within 2 hrs of the blood collection, separate plasma via centrifugation in the following manner:**
  - **Centrifuge vacutainer tube for 10 minutes at 2000 RCF preferably at refrigerated temperature.**
  - **Carefully aspirate the supernatant (plasma) taking care not to disrupt the cell layer.**
- **Aliquot plasma into a labeled cryogenic vial and leave remaining pellet in vacutainer tube.**
- **Label the cryogenic vials and vacutainer tubes with the study drug ID (4 digit code), time and date of blood collection.**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# Data Collection Procedures

- **Complete the ESETT PK Blood Collection eCRF in WebDCU™ within 5 days of enrollment. The eCRF will capture: height, the sample ID (4 digit), subject ID (4 digit), date, time, and whether the PK sample was taken from the same site as the study drug infusion for each sample.**
  - **Record any procedural deviations under Question 8. An example would be a sample processed outside of the specified time window.**
- **Samples collected outside of the sampling time windows or with smaller volumes than indicated are still useable and should be retained and shipped.**

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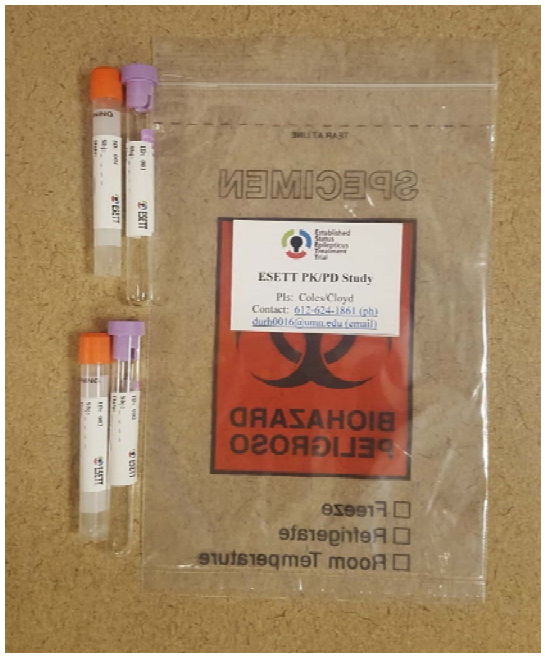
# Blood Sample Storage

- **Store cryogenic vials and vacutainer tubes at -20°C or lower until shipment.**

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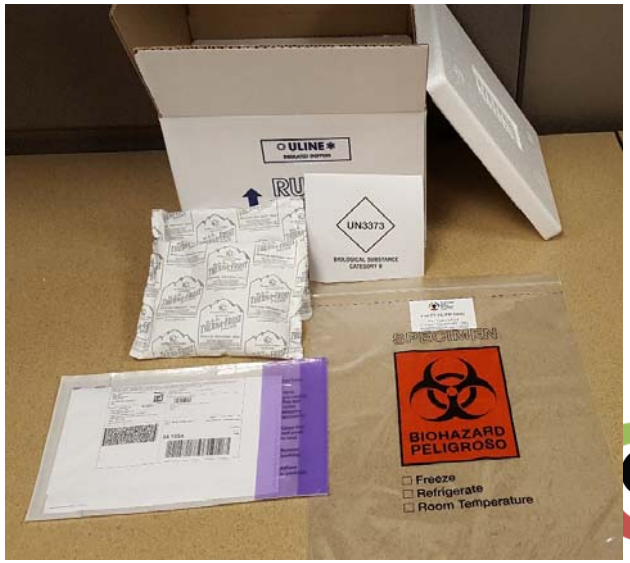
# Sample Shipping

- **A subject's samples can be shipped individually or batched. If batched, the samples should be shipped following the completion of up to 4 subjects or every 6 months, whichever comes first.**
- **Ship the study samples on cold packs provided (or dry ice) to the Center for Orphan Drug Research:**

**Usha Mishra, MS**

**University of Minnesota**
**Center for Orphan Drug Research**
**4-500 MTRF**
**2001 - 6th St SE**
**Minneapolis, MN 55455**

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# Sample Shipping

- **Send an email notification to esett-pkpd@umich.edu at time of shipment.**
- **Enter the shipping date and FEDEX tracking number into WebDCU™.**

- **Supplies will be automatically replenished based on enrollment activities. If you are concerned about your inventory, please contact esett-pkpd@umich.edu.**

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# Study Outcomes

- **Characterization of the exposure-response relationships.**
- **Provide guidance on how best to use FOS, LEV, and VPA for treatment of SE in children, adults, and elderly.**
- **Guide selection of optimal dose for future clinical trials.**

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# Frequently Asked Questions

- **Can a blood sample drawn from the drug infusion site be used?**
  - **Answer: No. Studies have shown that even with multiple flushing steps, drug concentrations are very often artificially high in such samples. If blood is inadvertently drawn from the drug infusion site, please discard sample and record in the PK blood collection eCRF. While this is a procedural deviation, it is NOT a protocol deviation.**
- **Can blood drawn from a site used to deliver fluids or other study medication be used?**
  - **Answer: Yes. Blood can be drawn from any site NOT used for study drug infusion.**
- **What should I do if we collect only one blood sample?**
  - **Answer: Process and ship the sample as specified. While we expect to obtain 2 samples from most subjects, a single sample from a subset of patients will still be valuable. This is NOT a protocol deviation.**
- **What should I do if we obtain the blood sample outside of the sampling time window?**
  - **Answer: The data from this sample can still be used. Record the actual time that the sample was collected on the PK blood collection eCRF and process and ship that sample as specified. While this is a procedural deviation, it is NOT a protocol deviation.**

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# Frequently Asked Questions

- **What should I do if the blood sample is centrifuged greater than 2 hrs after sample collection?**
  - **Answer: Record the procedural deviation under Question 8 of the PK blood collection eCRF. This is NOT a protocol deviation.**

- **What should I do if the volume of blood collected is less than 2.5 - 3 mL?**
  - **Answer: The sample will still be used. Process and ship the sample as specified. This is NOT a protocol deviation.**

- **What happens if I have misplaced or damaged the sample kit?**
  - **Answer: If pre-labeled vacutainer tubes or cryogenic vials are not available, you can use an EDTA-containing (lavender top) vacutainer tube for blood collection and a cryogenic vial or Eppendorf tube for the plasma sample available at your site. Tubes and vials should be labeled as specified in the Manual of Procedures.**

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# Contacts

- **ESETT PK/PD study team at esett-pkpd@umich.edu**
- **Lisa Coles at 612-624-1861 (office)**
- **James Cloyd at 612-624-4609 (office)**

# References

- **Manual of Procedures**
- **1 page quick guide**

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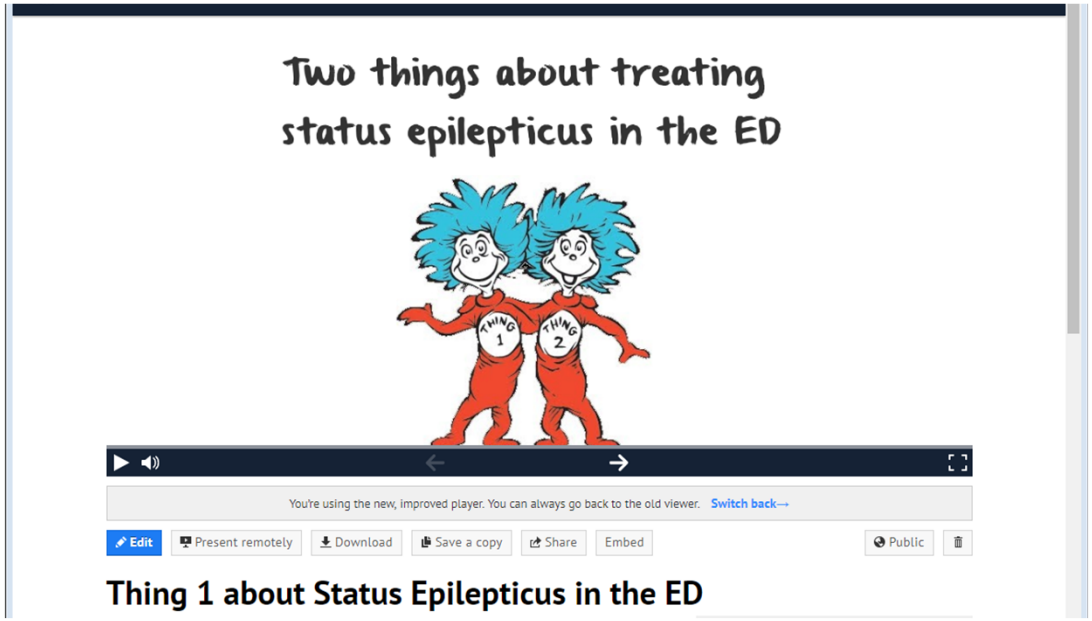
# Ongoing Training of Clinical Staff

- Peer-to-peer Best Practices from Sites
  - Amanda Lee, Children's Medical Center UTSW
  - Shannen Berry, Henry Ford Hospital
  - Barbara Davis, Christiana Hospital

# Ongoing Training of Clinical Staff

- Educational 5 minute module – preview and feedback
- http://goo.gl/JkVJ9o
- How to best use?



# 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
- Report the PATHOLOGY, not the outcome or treatment
  Not 'death' but the event that caused death

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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)

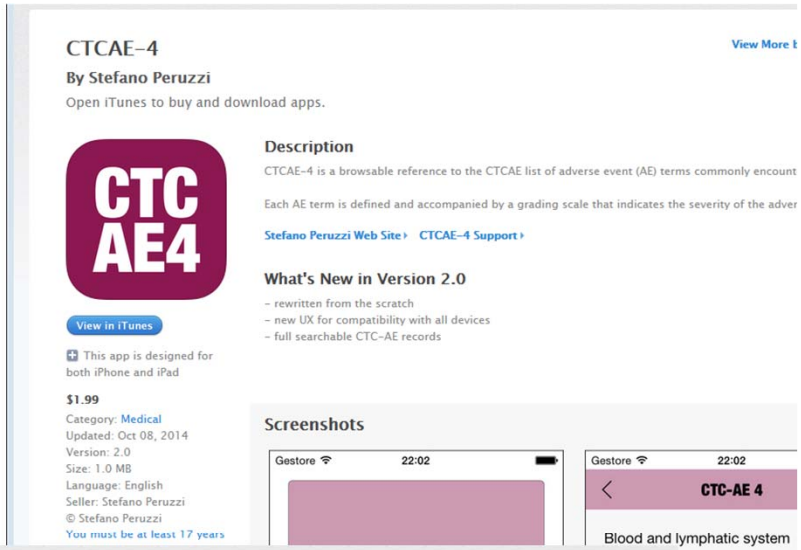
- Timing is suggestive.
- Not readily caused by something else
- This is something the intervention is known to cause.

**Definitely** (must have all 3)

- Timing suggests intervention caused the problem.
- No other possible cause.
- This is something the intervention is known to cause.

**E**stablished
**S**tatus
**E**pilepticus
**T**reatment
**T**rial


http://bioportal.bioontology.org/ontologies/MEDDRA


CTCAE-4
View More
By Stefano Peruzzi
Open iTunes to buy and download apps.
CTC AE4
Description
CTCAE-4 is a browsable reference to the CTCAE list of adverse event (AE) terms commonly encount
Each AE term is defined and accompanied by a grading scale that indicates the severity of the adver
Stefano Peruzzi Web Site
CTCAE-4 Support
What's New in Version 2.0
- rewritten from the scratch
- new UX for compatibility with all devices
- full searchable CTC-AE records
View in iTunes
This app is designed for both iPhone and iPad
$1.99
Category: Medical
Updated: Oct 08, 2014
Version: 2.0
Size: 1.0 MB
Language: English
Seller: Stefano Peruzzi
© Stefano Peruzzi
You must be at least 17 years
Screenshots
Gestore 22:02
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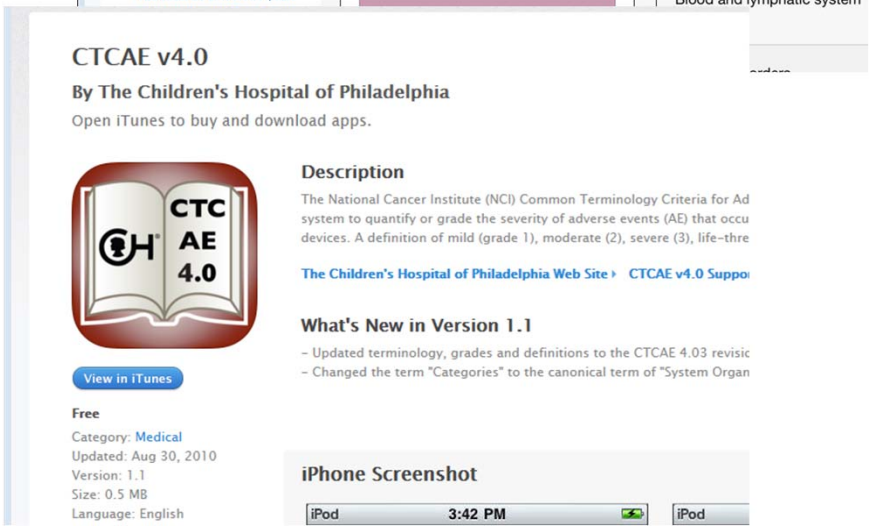
CTC-AE 4
Blood and lymphatic system


CTCAE v4.0
By The Children's Hospital of Philadelphia
Open iTunes to buy and download apps.
CTC AE 4.0
Description
The National Cancer Institute (NCI) Common Terminology Criteria for Ad
system to quantify or grade the severity of adverse events (AE) that occu
devices. A definition of mild (grade 1), moderate (2), severe (3), life-thre
The Children's Hospital of Philadelphia Web Site
CTCAE v4.0 Suppo
What's New in Version 1.1
- Updated terminology, grades and definitions to the CTCAE 4.03 revisic
- Changed the term "Categories" to the canonical term of "System Organ
View in iTunes
Free
Category: Medical
Updated: Aug 30, 2010
Version: 1.1
Size: 0.5 MB
Language: English
iPhone Screenshot
iPod 3:42 PM
iPod

# Write good SAE narratives

Tell a story

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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# How are SAE narratives used?

Medical safety monitor

FDA (occasionally)

DSMB

Study Leadership

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# Example

Depressed level of consciousness

A 42 yo with epilepsy and prior TBI had status epilepticus, received lorazepam 4 mg, and was enrolled on 3/1517 at 9:02PM. Seizures continued at 9:22PM and she received additional midazolam 5 mg. Seizures stopped. She remained sedated but was maintaining an airway at 10:02PM and was admitted to the ICU. She was endotracheally intubated in the ICU on 03/16/17 at 02:41 for airway protection due to continued decreased level of consciousness, and possibly respiratory depression. Extubated on 03/16/17 at 07:50 am without complication.

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# Narrative template - intubation

A [age] year old with [concise relevant history, e.g. epilepsy] had status epilepticus, received [benzodiazepine, dose, route], and was enrolled on [date] at [time]. Seizures [stopped/continued]. [Additional treatment, dose, route, time, response]. Because of [continued seizures / persistent decreased consciousness / respiratory depression / hypoxia / hypercarbia / other], endotracheal intubation was performed at [time] with [induction and paralytic agents] and then sedated with [agent]. Admitted to the ICU. [Extubated [on date] [at time] / Remained intubated as of [date] because of [suspected etiology]]

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# Another example

Respiratory Depression

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

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# Too much

35 y.o. male with a history of anxiety, bipolar affective disorder, schizophrenia, and previous seizure event thought to be EtOH related presented to enrolling center ED via EMS 2/8/17 at 20:47 with seizures. Seizure in route abated with 4mg midazolam IM EMS administered. On initial assessment patient was sedated, but responded to noxious stimuli. Sedation thought to be due to EtOH, versed, and post-ictal state. Labs and CT head ordered. In CT patient had repeat seizure. He was given midazolam 3 mg IM and was brought back to ER. He appeared to continue to be having seizure so additional midazolam 3 mg IV was given. Seizure appeared to resolve. Neurology consulted to ER. Patient return of seizures occurred at approximately 2240. He was given an additional lorazepam 2 mg IV. Seizure continued for 5 minutes so ESETT drug was given. Study drug infusion started at 23:01. During infusion, pt appeared to have aspiration event. Infusion completed and patient stopped seizing and withdrew from nailbed pressure. At 20 minute assessment he was still responding to noxious stimulation. He was intubated for airway protection due to apparent aspiration event. He was sedated with propofol post intubation. Pt was admitted to the ICU for further diagnosis and management. 60 minute assessment at 00:15 revealed pt was sedated but withdrew from nailbed pressure. On 2/10/17 about 13:15 he was electively extubated. 2/10/17 1900 many verbally aggressive outbursts noted. 2/11/17 09:03 patient left AMA, after psychiatric evaluation

**E**stablished
**S**tatus
**E**pilepticus
**T**reatment
**T**rial

# Too much - continued

35 y.o. ~~male~~ with ~~a history of anxiety, bipolar affective disorder, schizophrenia,~~ complex psychiatric history and ~~previous seizure event thought to be EtOH related~~ and prior alcohol related seizures…

~~presented to enrolling center ED via EMS 2/8/17 at 20:47 with seizures. Seizure in route abated with 4mg midazolam IM EMS administered. On initial assessment patient was sedated, but responded to noxious stimuli. Sedation thought to be due to EtOH, versed, and post-ictal state. Labs and CT head ordered. In CT patient had repeat seizure. He was given midazolam 3 mg IM and was brought back to ER. He appeared to continue to be having seizure so additional midazolam 3 mg IV was given. Seizure appeared to resolve. Neurology consulted to ER. Patient return of seizures occurred at approximately 2240. He was given an additional lorazepam 2 mg IV. Seizure continued for 5 minutes so ESETT drug was given. Study drug infusion started at 23:01. During infusion, pt appeared to have aspiration event.~~

…had stuttering status epilepticus, received midazolam 10 mg and lorazepam 2 mg in divided doses over 2 hours, and enrolled on 2/8/17 at 23:01, followed by an aspiration event and transient hypoxia. ….

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# Too much - continued

~~Infusion completed and patient stopped seizing and withdrew from nailbed pressure. At 20 minute assessment he was still responding to noxious stimulation. He was intubated for airway protection due to apparent aspiration event.~~

He stopped seizing but remained poorly responsive. He was endotracheally intubated at 23:25 for airway protective and decreased level of consciousness and risk of further aspiration.

~~He was sedated with propofol post intubation. Pt was admitted to the ICU for further diagnosis and management. 60 minute assessment at 00:15 revealed pt was sedated but withdrew from nailbed pressure.~~

He was sedated with propofol and admitted to ICU. Normal CXR and no sequelae of aspiration on 2/9/17.

~~On 2/10/17 about 13:15 he was electively extubated. 2/10/17 1900 many verbally aggressive outbursts noted. 2/11/17 09:03 patient left AMA, after psychiatric evaluation~~

Extubated on 2/10/17.

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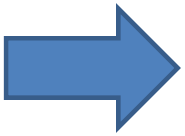
# Too much - resolution

35 y.o. male with a history of anxiety, bipolar affective disorder, schizophrenia, and previous seizure event thought to be EtOH related presented to enrolling center ED via EMS 2/8/17 at 20:47 with seizures. Seizure in route abated with 4mg midazolam IM EMS administered. On initial assessment patient was sedated, but responded to noxious stimuli. Sedation thought to be due to EtOH, versed, and post-ictal state. Labs and CT head ordered. In CT patient had repeat seizure. He was given midazolam 3 mg IM and was brought back to ER. He appeared to continue to be having seizure so additional midazolam 3 mg IV was given. Seizure appeared to resolve. Neurology consulted to ER. Patient return of seizures occurred at approximately 2240. He was given an additional lorazepam 2 mg IV. Seizure continued for 5 minutes so ESETT drug was given. Study drug infusion started at 23:01. During infusion, pt appeared to have aspiration event. Infusion completed and patient stopped seizing and withdrew from nailbed pressure. At 20 minute assessment he was still responding to noxious stimulation. He was intubated for airway protection due to apparent aspiration event. He was sedated with propofol post intubation. Pt was admitted to the ICU for further diagnosis and management. 60 minute assessment at 00:15 revealed pt was sedated but withdrew from nailbed pressure. On 2/10/17 about 13:15 he was electively extubated. 2/10/17 1900 many verbally aggressive outbursts noted. 2/11/17 09:03 patient left AMA, after psychiatric evaluation



A 35 yo with complex psychiatric history and prior alcohol related seizures had stuttering status epilepticus, received midazolam 10 mg and lorazepam 2 mg in divided doses over 2 hours, and enrolled on 2/8/17 at 23:01, followed by an aspiration event and transient hypoxia. He stopped seizing but remained poorly responsive. He was endotracheally intubated at 23:25 for airway protective and decreased level of consciousness and risk of further aspiration. He was sedated with propofol and admitted to ICU. Normal CXR and no sequelae of aspiration on 2/9/17. Extubated on 2/10/17.

# Not enough

- Blood culture positive for beta hemolytic strep, left peripheral line. Patient started Levaquin 750 mg oral tablet qd x 10 days

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# ~~Not~~ enough

- ~~Blood culture positive for beta hemolytic strep, left peripheral line. Patient started Levaquin 750 mg oral tablet qd x 10 days~~

- A 42 yo with epilepsy and prior TBI was enrolled on 3/15/17 at 9:02PM. On [date?] she had fever, leukocytosis, and underwent a workup for an infectious source. Blood culture grew strep agalactiae sensitive to ceftriaxone and levofloxacin, but no other source was found. She was treated with ceftriaxone IV x 4 days, and levofloxacin PO x 10 days, and had no further fevers.

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# Style points

- Use generic drug names
- Use a spell checker
- Have the site PI read critically

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Many Thanks!