ESETT

Established Status Epilepticus Treatment Trial (ESETT)

A multicenter, randomized, blinded, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam in the emergency department treatment of patients with benzodiazepine-refractory status epilepticus.

ESETT planning group

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Synopsis

- 150,000 Episodes of Status Epilepticus
- 30% continue to seizure after benzodiazepines
- Best second line agents unknown

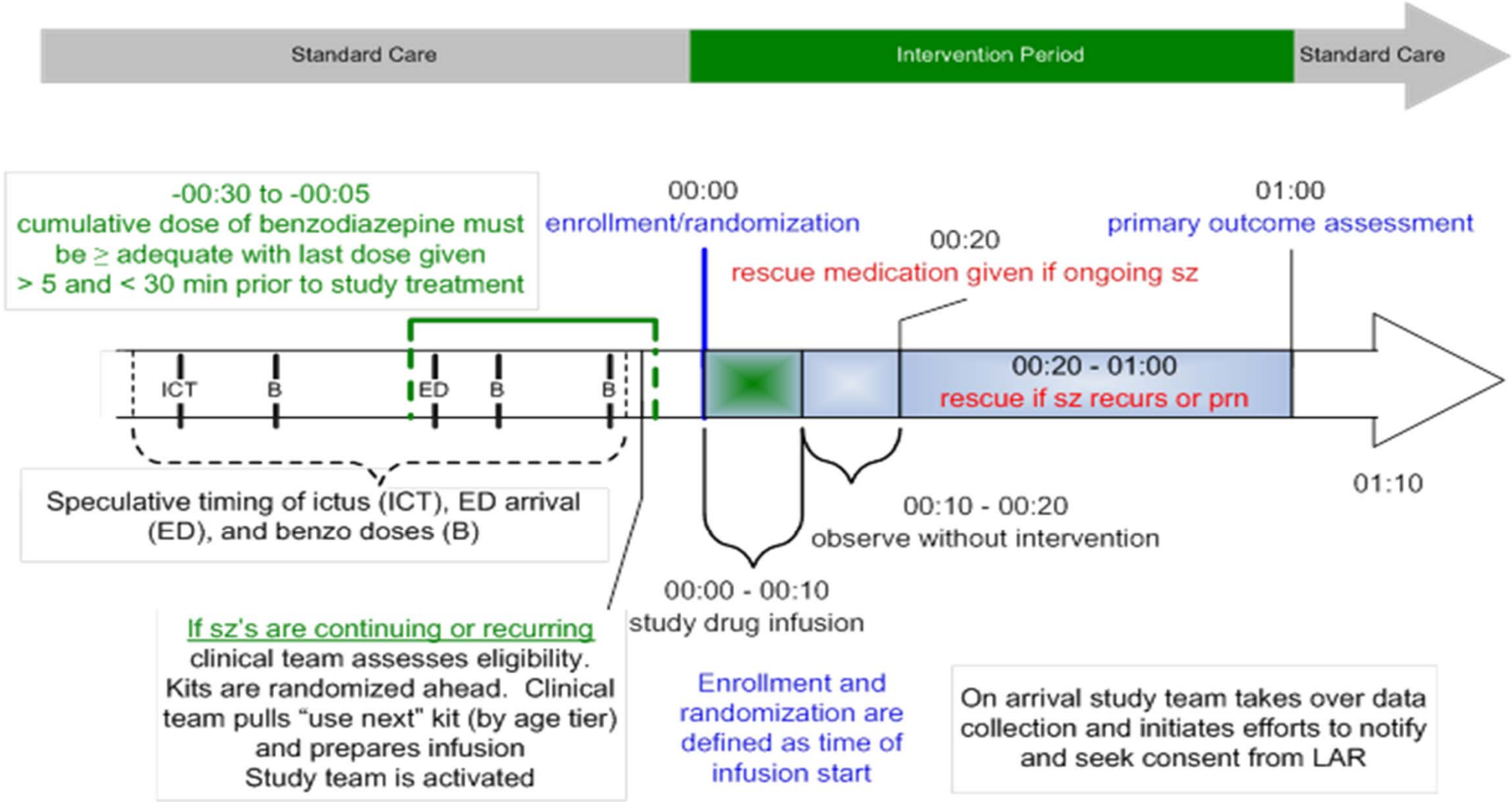
- Three agents are commonly used
  - Fosphenytoin (FOS) 20 mg/Kg
  - Levetiracetam (LEV) 40 mg/Kg
  - Valproic acid (VPA) 60 mg/Kg

Inclusion Criteria

Inclusion criteria	Measure
Patient witnessed to have a seizure in the past 5-30 minutes.	Time of first seizure is when EMS personnel were called if eyewitness account available or first seizure witnessed by EMS personnel.
Patient received adequate dose of benzodiazepines in the past 5-30 minutes. The doses may be divided. Time is counted from the last dose.	EMS or ED record of treatment: For those > 40 kg--diazepam 10 mg IV or rectal, lorazepam 4 mg, IV, or midazolam 10 mg IM or IV. For those 10-40 Kg adequate doses are: diazepam 0.3 mg/kg IV or rectal, lorazepam 0.1 mg/kg IV or midazolam 0.3 mg/kg IM or 0.2 mg/Kg IV
Continueded seizure in the Emergency Department	Clinical observation
Age more than 2 years	Caretakers report the age or clinical observation

Exception From Informed Consent

- **Justification:**
  - Convulsive status epilepticus is a life threatening disease
  - Best available treatment is unproven
  - Clinical trials are needed
  - Obtaining prospective informed consent is not feasible
    - Subject altered (actively seizing and unconscious)
    - An acute seizing patient cannot be identified prospectively
    - LAR is often not available in the short time frame required. Even when an LAR is available, **meaningful informed consent is impossible to obtain** because of the time constraints and the emotional distress caused by witnessing convulsive SE.
  - Subjects may benefit from the research
  - Research could not be carried out without EFIC
  - Therapeutic window too short


Standard Care
Intervention Period
Standard Care
-00:30 to -00:05
cumulative dose of benzodiazepine must be ≥ adequate with last dose given
> 5 and < 30 min prior to study treatment
00:00
enrollment/randomization
00:20
rescue medication given if ongoing sz
01:00
primary outcome assessment
ICT
B
ED
B
B
00:20 - 01:00
rescue if sz recurs or prn
01:10
Speculative timing of ictus (ICT), ED arrival (ED), and benzo doses (B)
00:10 - 00:20
observe without intervention
00:00 - 00:10
study drug infusion
If sz's are continuing or recurring
clinical team assesses eligibility.
Kits are randomized ahead. Clinical team pulls "use next" kit (by age tier) and prepares infusion
Study team is activated
Enrollment and randomization are defined as time of infusion start
On arrival study team takes over data collection and initiates efforts to notify and seek consent from LAR

Primary Outcome

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.

(*Note if patient is intubated within 60 minutes of enrollment, it is failure to meet primary outcome, because sedatives are used)

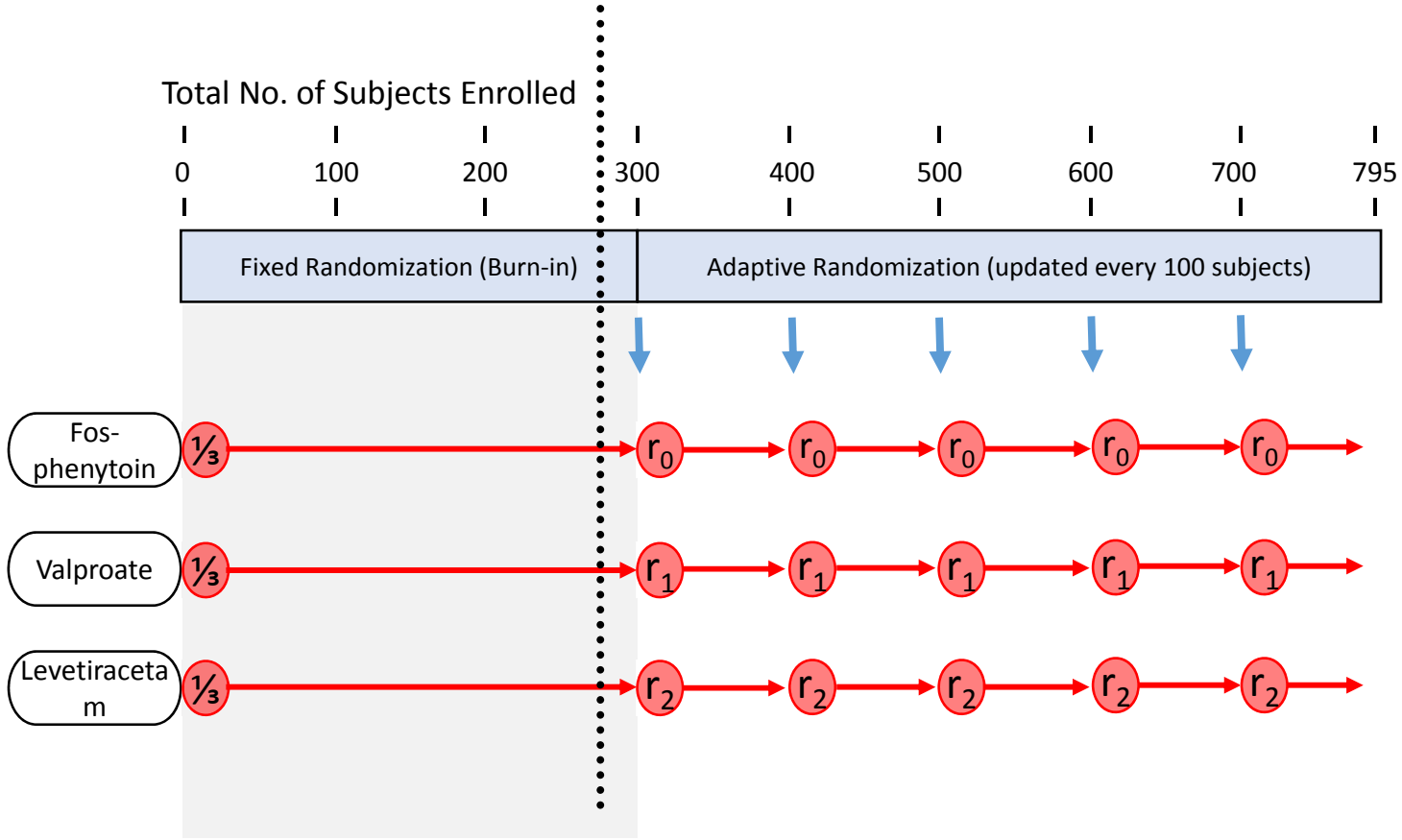
Other Outcomes

Safety outcomes

- Life-threatening hypotension:
- Life-threatening cardiac arrhythmia:

Secondary

- Richmond agitation and sedation score at primary outcome determination
- Time to termination of seizures
- Intubation,
- Admission to ICU
- Seizure recurrence
- Length of stay in the ICU and hospital,
- Mortality



Red circles in columns indicate randomization probabilities

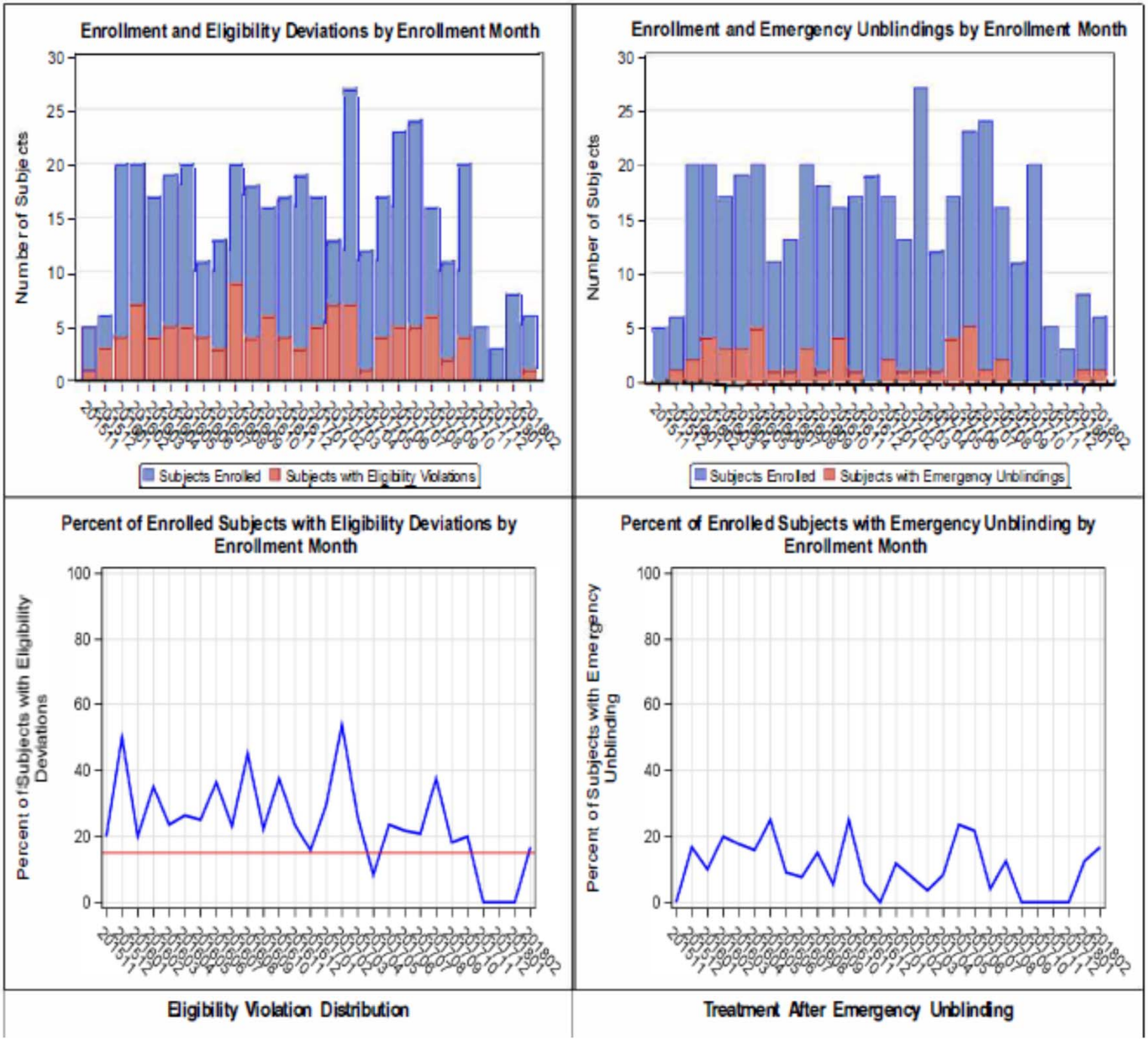
Blue arrows indicate updates that occur every 100 subjects (about every 6 months)

Starting at n=400, each update asks about early stopping:

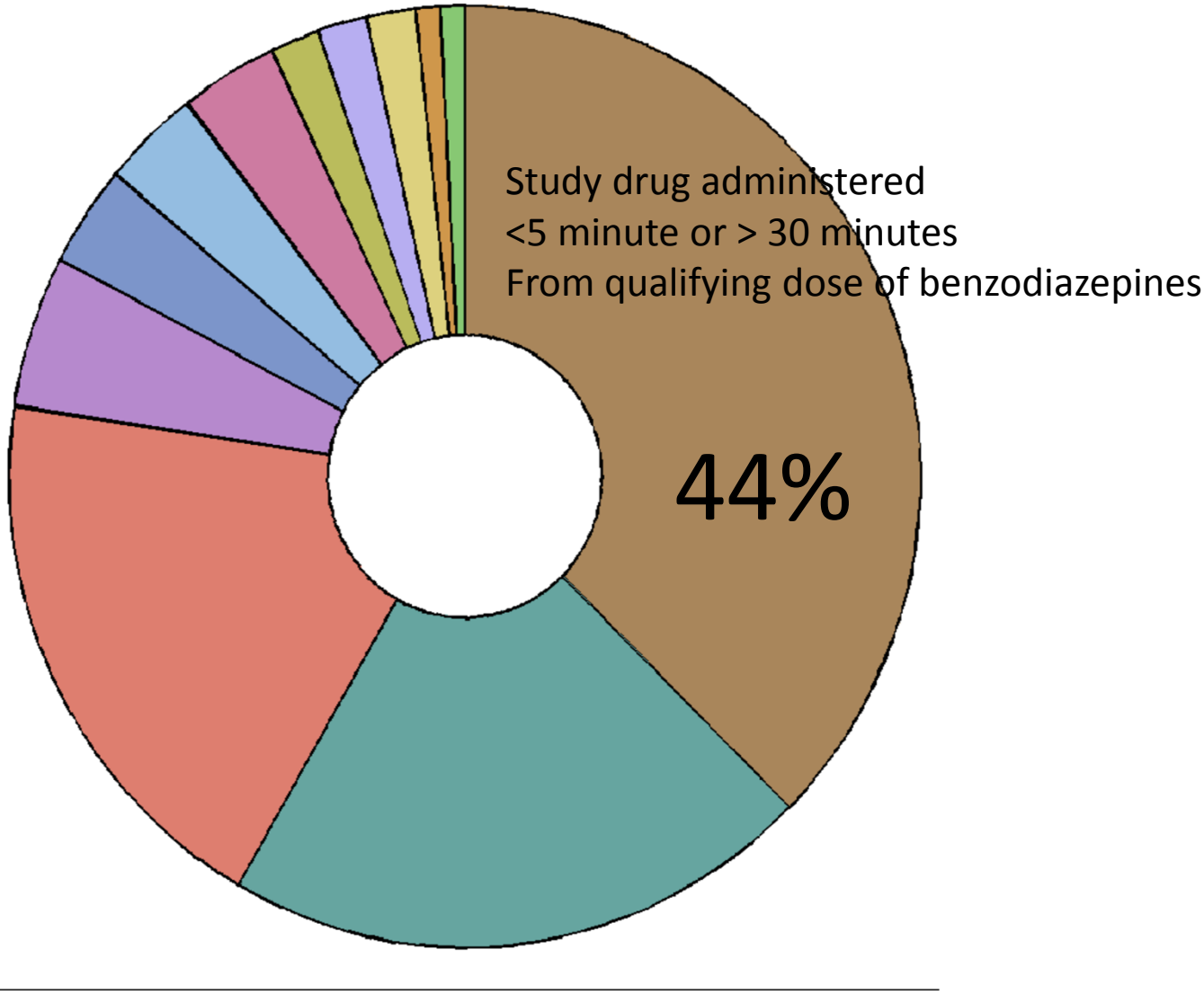
Are they all the same? Is the predicted prob of finding winner or loser < 0.05?

Do none of them work? Is the predicted prob < 0.05 that any agent's response rate >25%

Do we have a winner? Is the predicted prob >0.975 that any arm is the most effective?


Enrollment and Eligibility Deviations by Enrollment Month
Number of Subjects
Subjects Enrolled
Subjects with Eligibility Violations
Enrollment and Emergency Unblindings by Enrollment Month
Number of Subjects
Subjects Enrolled
Subjects with Emergency Unblindings
Percent of Enrolled Subjects with Eligibility Deviations by Enrollment Month
Percent of Subjects with Eligibility Deviations
Percent of Enrolled Subjects with Emergency Unblinding by Enrollment Month
Percent of Subjects with Emergency Unblinding
Eligibility Violation Distribution
Treatment After Emergency Unblinding

Nature of deviations



Timing of benzodiazepines

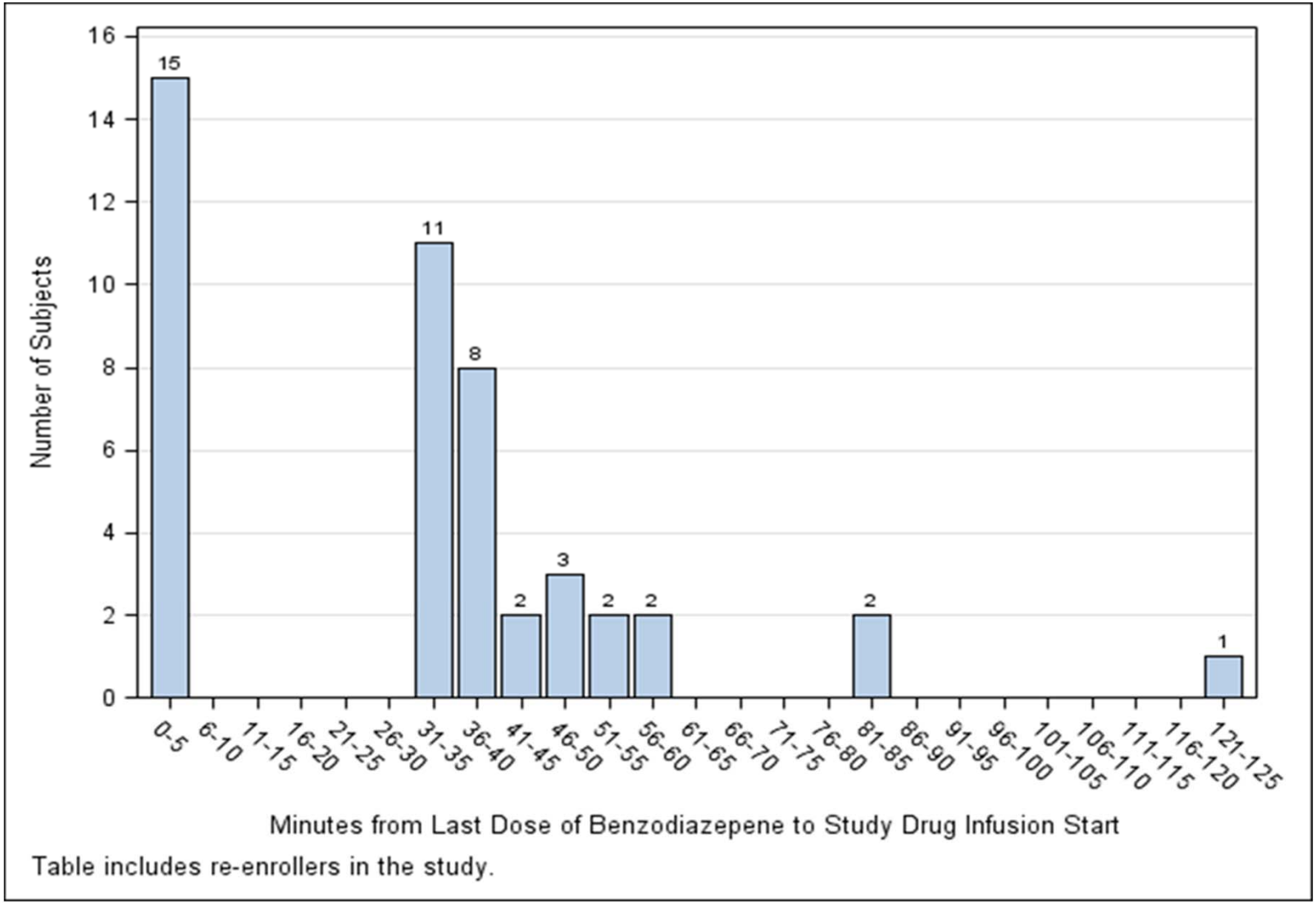
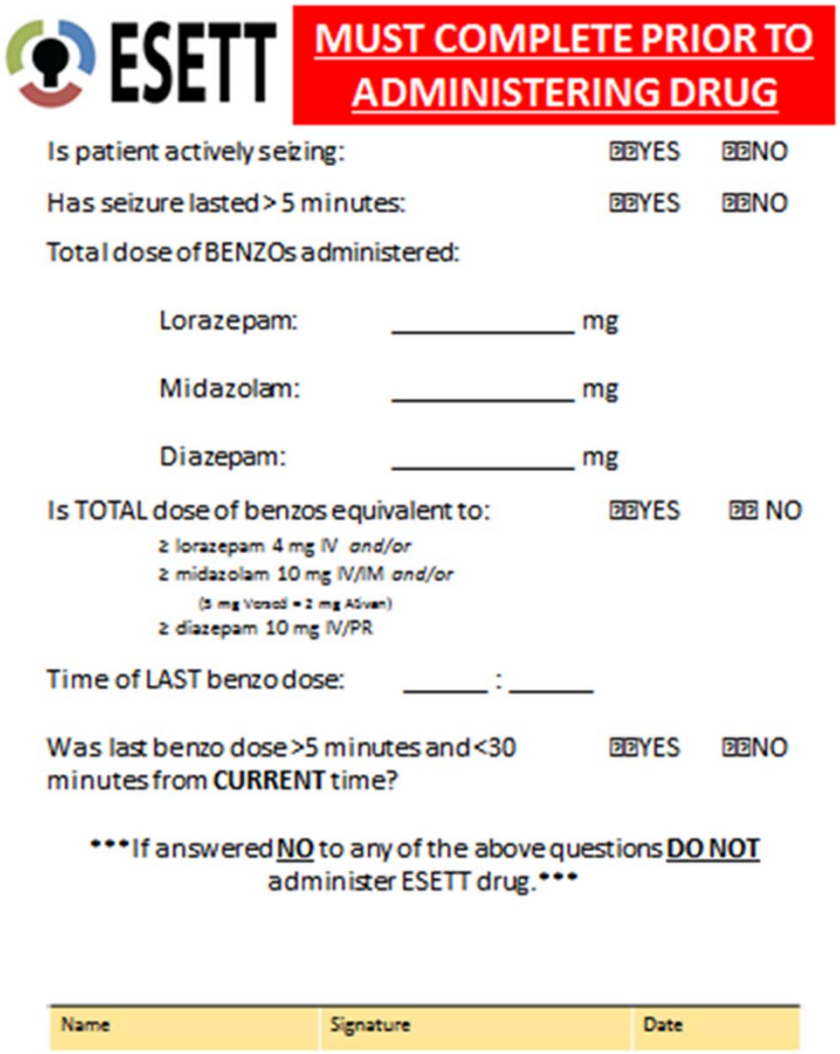


Table includes re-enrollers in the study.

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 ASivan)
≥ diazepam 10 mg IV/PR

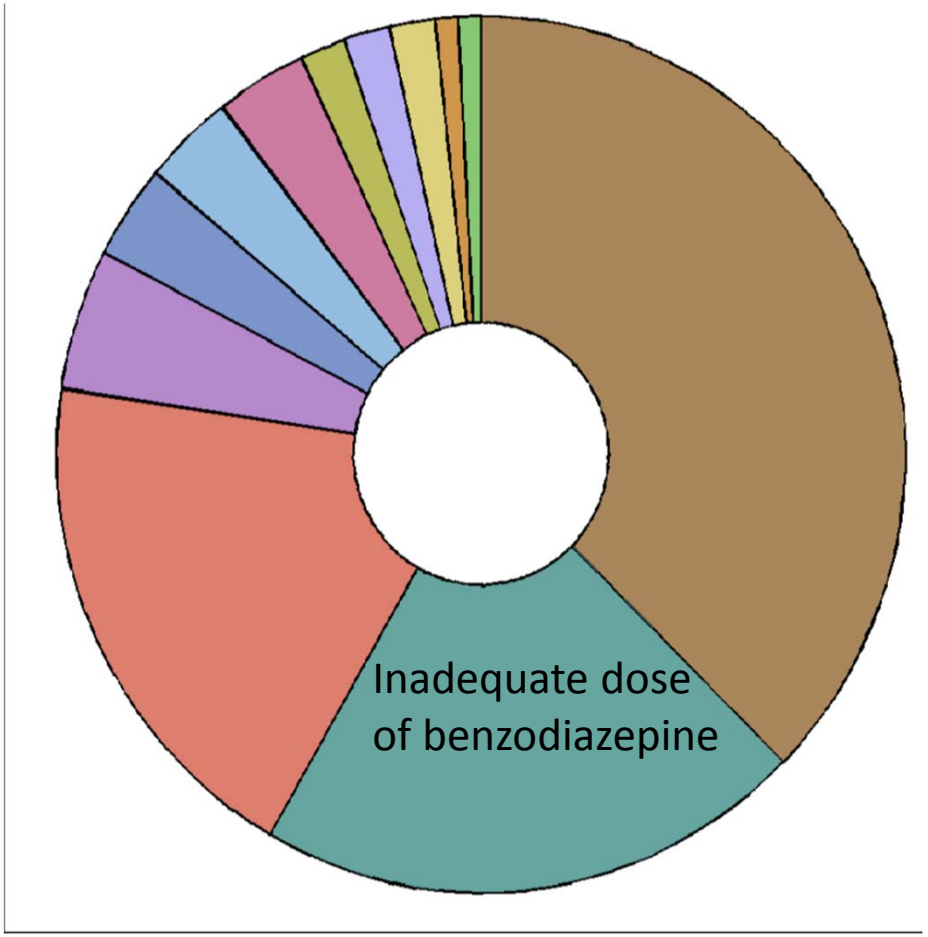
Time of LAST benzo dose: _____ : _____

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.

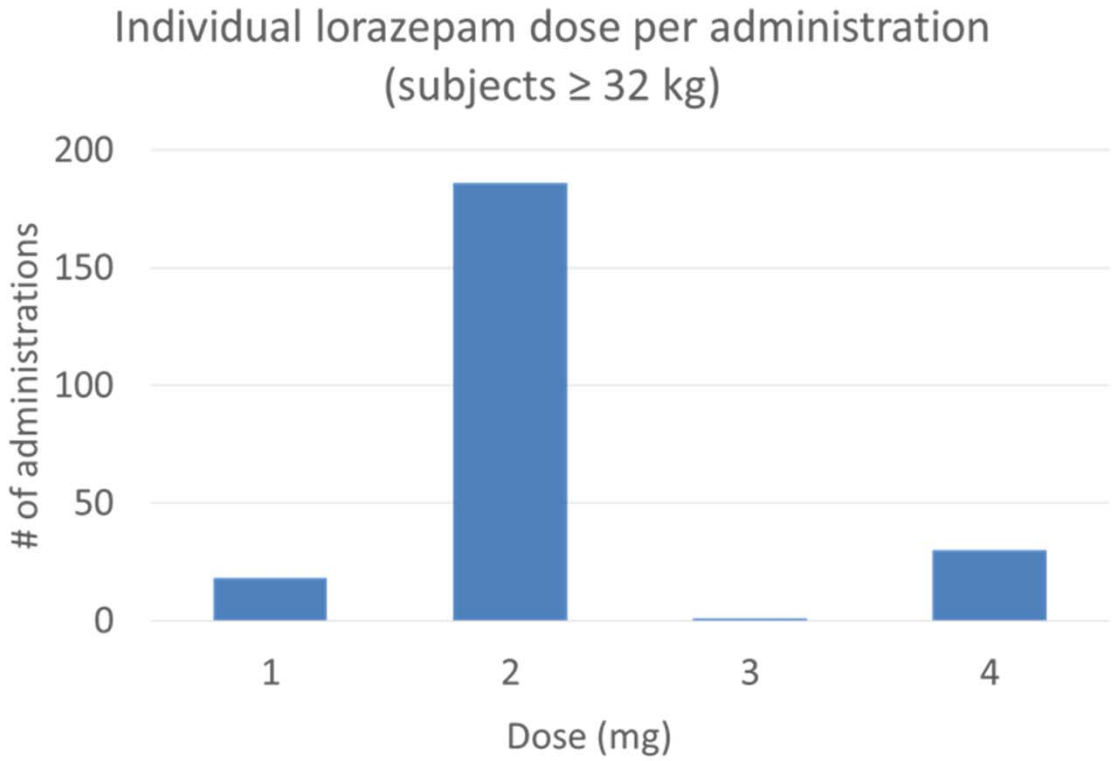
Name	Signature	Date

Causes of enrollment violations



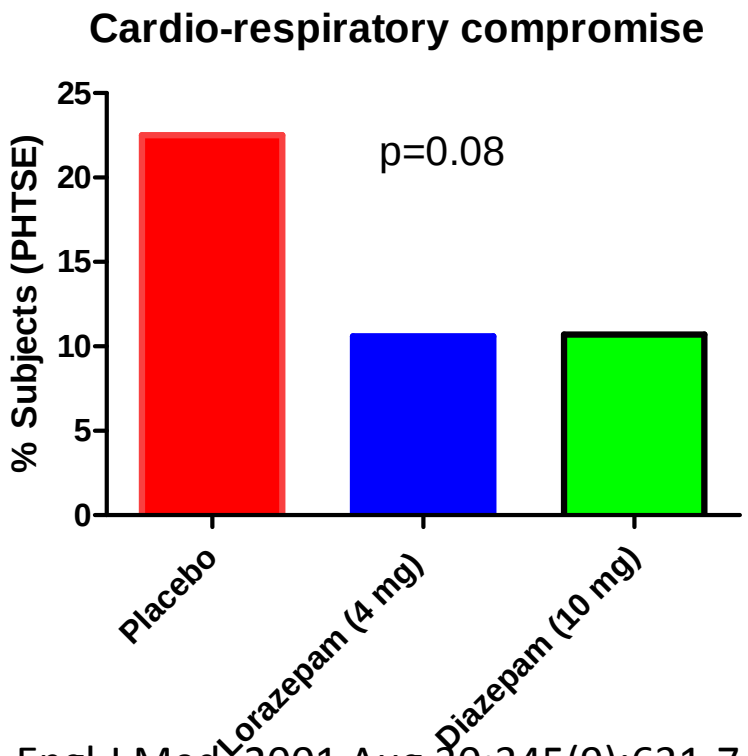
Under-dosing Benzodiazepine: a common practice

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



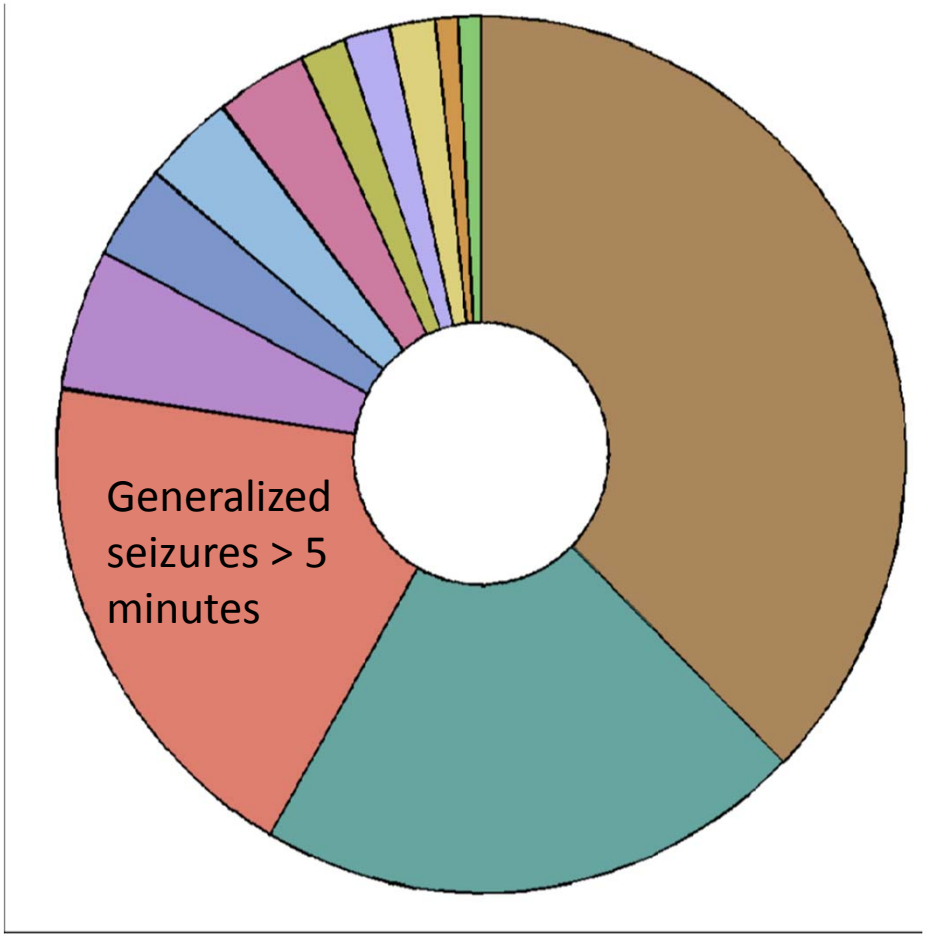
Small dose safer or more dangerous?

- 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 enrollment violations

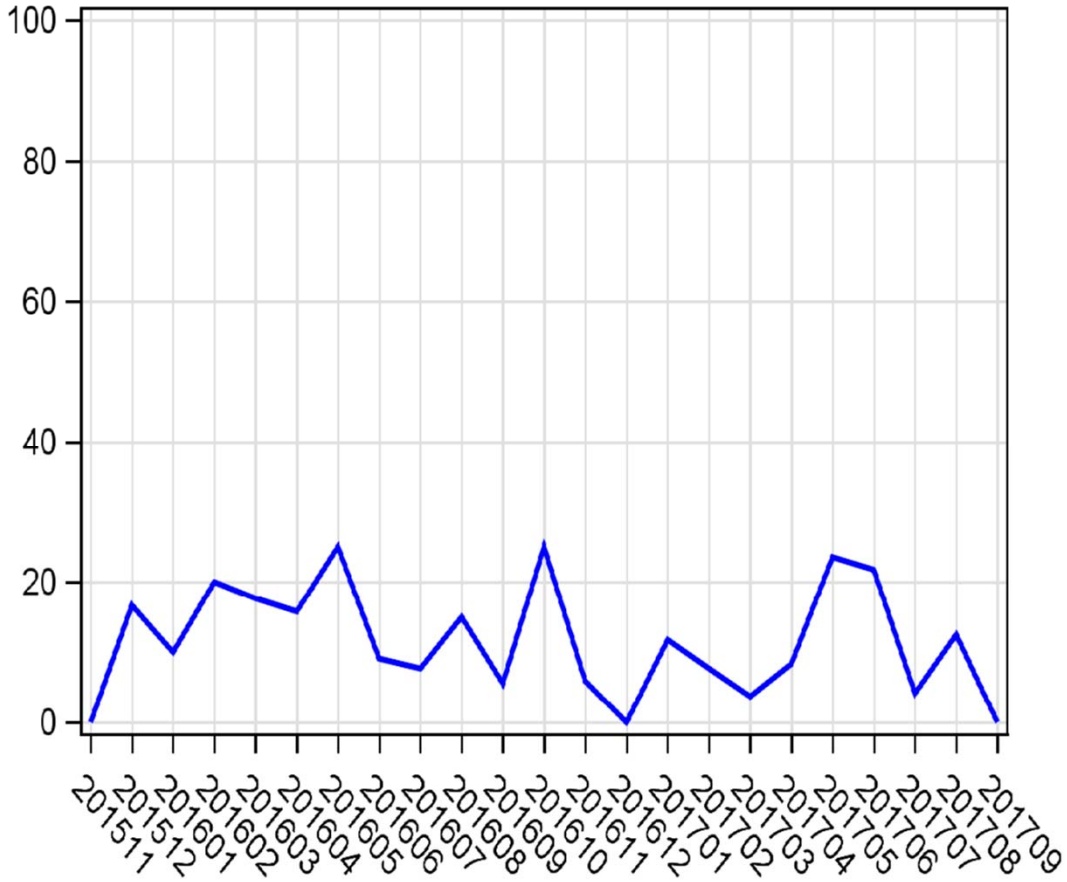


GTCS > 5 minutes

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

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?



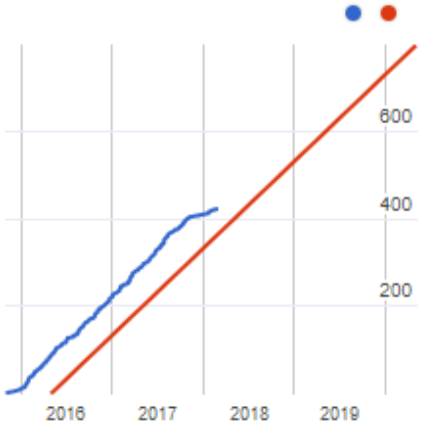
Emergency unblinding

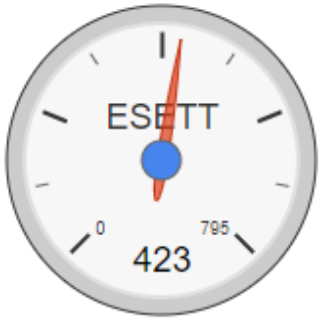
- After any unnecessary emergency unblinding the site PI will be contacted. Site PI will decide on a corrective action plans such as reeducation.

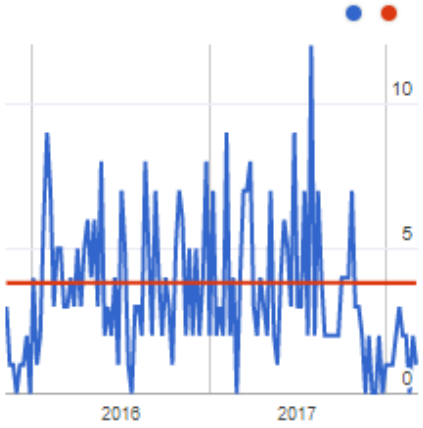
400 Subjects

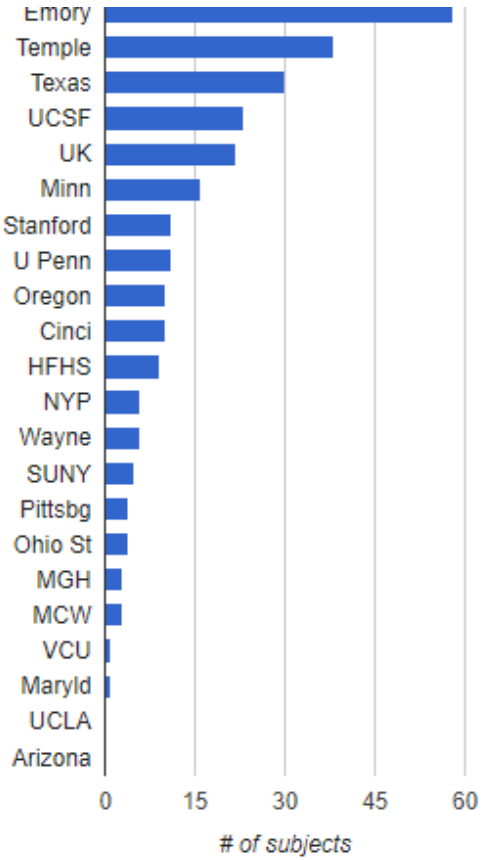
- At our first interim analysis at 400 subjects, we have met a predefined stopping rule in the overall patient cohort, however, there was also evidence of a possible interaction with age.
- Our analysis plan includes a contingency to divide our analysis into pediatric and adult cohorts if they appear to be different and analyze separately for futility.
- The DSMB has approved our request to activate this contingency. Evaluated separately, the adult age tiers still meet our predefined stopping rule, but the pediatric tier does not yet.
- Therefore, enrollment of adults in ESETT has now ended, but enrollment of children will continue.

Accrual – tracking









You can always see up to the minute accrual data at:

nett.umich.edu/nett-resources/dashboard

or go to nett.umich.edu and click on “enrollment dashboard”

Acknowledgments

Lab Colleagues

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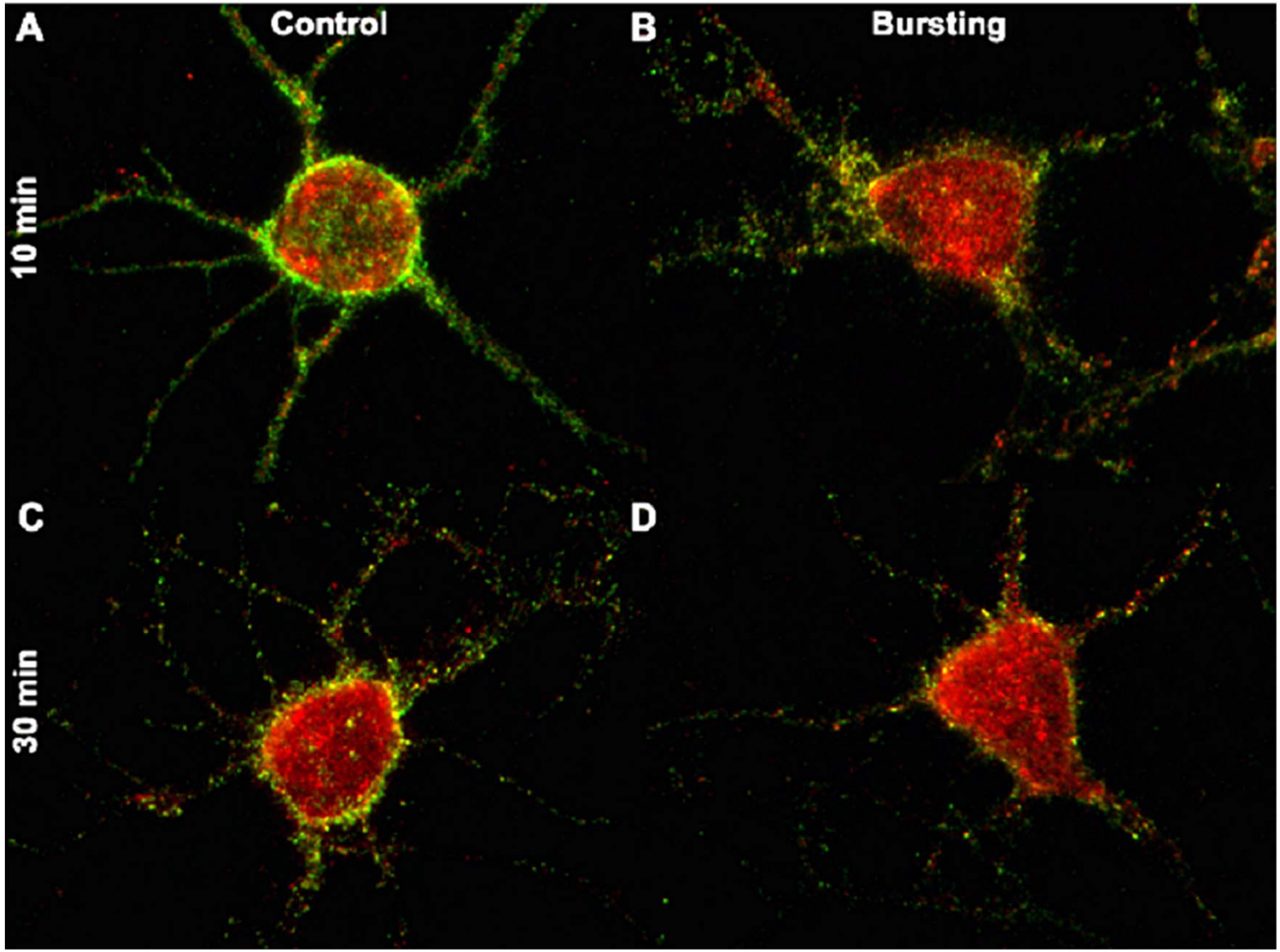
In vitro bursting (High K /NMDA)



120min Somatosensory cortex