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.
**History of the trial**

**14:00-14:30** What is the relative value of the standard anticonvulsants: phenytoin and fosphenytoin, valproate, phenobarbital, levetiracetam? Eugen Trinka (Innsbruck, Austria)

**14:30-15:00** Pharmacodynamic and pharmacokinetic characteristics of intravenous drugs in status epilepticus Meir Bialer (Jerusalem, Israel)

**15:30-18:00** Clinical trials in SE
Chairs: Michel Baulac (Paris, France)
Matthew Walker (London, United Kingdom)
ESETT: Europe & US 2009-2010

Hannah Cock

HTA outline application – ESETT Flow Diagram participants and study design

This is a sequential (adaptive) trial design. Numbers shown are maximums; actual numbers may be considerably fewer.

- Assess eligibility
  - A clinical diagnosis of convulsive status epilepticus (continuous or intermittent convulsions without regaining consciousness lasting >5 minutes)
  - have received benzodiazepine treatment to maximum recommended doses

  yes
  No: give additional benzodiazepine to maximum recommended doses. Seizures continuing?

  no

Age ≥5 years, fulfil additional inclusion/exclusion criteria

Randomization (pre-filled boxes in A&E)
N = 1740

- i.v. Phenytoin (n=580)
  18mg/kg @50mg/min

- i.v. Valproate (n = 580)
  30mg/kg @10mg/kg/min

- i.v. Levetiracetam (n = 40mg/kg @6mg/kg/min)

Follow up: 0-2 hours (treating clinician; n = 1740)

- Clinical observations at least every 30 mins: Seizure activity (motor features, nystagmus, movements, level of consciousness); HR, oxygen saturations and BP
- Additional investigations and any non-seizure treatment as required/standard care
- If seizures continue/recur, proceed with usual care (in most instances intubation and anesthesia)
- When patient clinically stable, register on line (demographics, known comorbidities, CSE prior to randomised treatment, previous epilepsy y/n/unknown), treatment and time initiation, time seizure cessation.
2. Our colleagues in Europe (including Hannah Cock, Simon Shorvon and Tim Coats from the U.K. and Eugen Trinka from Austria) are making definite progress with their plans for ESETT (European Status Epilepticus Treatment Trial). Based on discussions we had at the last SE Colloquium held in Innsbuck in April, there was a strong consensus that it would be best if the European trial was carried out jointly with centers in the U.S., given the likely number of study subjects and the desire to complete the study as rapidly as possible. The Europeans have already determined there is a reasonably good chance they can find funding for the study from within the U.K., but rules on indemnification will prevent any funds going to the U.S.
3. The RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial) study, which has been implemented within the NINDS-supported Neurology Emergency Treatment Trials (NETT) network, is enrolling patients at a faster than expected rate and may well be completed within 12-18 months. The NETT is therefore looking for opportunities to support the next SE study sooner than later.
4. Preliminary discussions with NINDS leadership have indicated that the institute is very interested in supporting a SE study of the type we are considering.
ESETT planning group

Bleck       Cock       Chamberlain   Cloyd       Elm        Fountain
Fureman     Lowenstein  Shinnar      Silbergleit  Treiman    Trinka
Rationale
Status Epilepticus: Epidemiology

Status epilepticus: a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness.

Incidence 41-61/100,000.

Episodes of status epilepticus in US in 2010: 120,000-188,459.

Mortality in patients with status epilepticus to 17%. Mortality correlates with cause & duration of SE.

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Graph showing incidence per 100,000 for different age groups (1, 5, 10, 15, 40, 60, 80, >80).

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DeLorenzo et al. Neurology 1996
Effects of Fever Associated Status Epilepticus in Children: FEBSTAT

1) 11% incidence of Hippocampal injury (T2 signal increase) compared to 0% in control (febrile seizures).

2) Hippocampal T2 hyperintensity after FSE represents acute injury often evolving to a radiological appearance of HS after 1 year.

Shinnar et al. Neurology 2012
Lewis et al. Annals of Neurology 2014
Benzodiazepines: Initial Treatment

IM midazolam vs IV lorazepam

Point Estimates (95% CI)

- $P_{IM} = 0.73$ (0.69–0.78)
- $P_{IV} = 0.63$ (0.59–0.68)

Lorazepam vs diazepam for pediatric status epilepticus
Need for Trial

- There is no well-controlled prospective clinical trial to guide the treatment of SE in patients who fail benzodiazepines.
- SE not responding to benzodiazepines is called Established Status Epilepticus (ESE).
- Episodes of SE in US in 2010: 41-61/100,000 X 309 million = 120,000-188,459
- 35-45% of patients with convulsive SE do not respond to benzodiazepines i.e. 42-72,000 ESE patient.
## Therapy of Established SE: Real world choices

<table>
<thead>
<tr>
<th>Property/AED</th>
<th>Fosphenytoin</th>
<th>Levetiracetam</th>
<th>Valproic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popularity of use in the US</td>
<td>Most commonly used (60-65%)</td>
<td>Used often (20-30)</td>
<td>Least often</td>
</tr>
<tr>
<td>Ease of administration</td>
<td>Slow</td>
<td>Fast</td>
<td>Fast</td>
</tr>
<tr>
<td>Speed of action</td>
<td>Slow administration</td>
<td>Enters brain slowly, acts slowly</td>
<td>Yes</td>
</tr>
<tr>
<td>Action last long</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Efficacious in animal models</td>
<td>Least effective</td>
<td>In combination with diazepam</td>
<td>Very effective</td>
</tr>
<tr>
<td>Terminates seizures</td>
<td>Partial seizures</td>
<td>Partial and generalized</td>
<td>Partial and generalized</td>
</tr>
<tr>
<td>Safe</td>
<td>Hypotension, cardiac arrhythmia.</td>
<td>safe</td>
<td>Safe for acute use</td>
</tr>
</tbody>
</table>
EFIC

• 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
## Inclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient witnessed to have a seizure in the past 5-30 minutes.</td>
<td>Time of first seizure is when EMS personnel were called if eyewitness account available or first seizure witnessed by EMS personnel.</td>
</tr>
<tr>
<td>Patient received adequate dose of benzodiazepines in the past 5-30 minutes.</td>
<td>EMS or ED record of treatment: For those &gt; 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</td>
</tr>
<tr>
<td>Continueded seizure in the Emergency Department</td>
<td>Clinical observation</td>
</tr>
<tr>
<td>Age more than 2 years</td>
<td>Caretakers report the age or clinical observation</td>
</tr>
</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
<th>Supporting References</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOS</td>
<td>20 mg/kg (PE) with maximum 1500 mg</td>
<td>Viewed as standard dose.</td>
<td>PDR: Package insert</td>
</tr>
<tr>
<td>LEV</td>
<td>60 mg/kg with max 4500 mg</td>
<td>Highest approved dose for children, Published reports suggest safety of 4500 mg.</td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>40 mg/kg with max 3,000 mg</td>
<td>Doses ranging between 15-45 mg/kg have been reported.</td>
<td>Limdi, et al (2007)</td>
</tr>
</tbody>
</table>
-00:30 to -00:05 cumulative dose of benzodiazepine must be ≥ adequate with last dose given > 5 and < 30 min prior to study treatment.

Speculative timing of ictus (ICT), ED arrival (ED), and benzo doses (B).

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.

Onset of < 30 min: -00:05 - 00:20
-00:10 - 00:20 observe without intervention
-00:20 - 01:00 rescue if sz recurs or prn
-01:00 primary outcome assessment
-01:10

Primary entrance to study
-00:00 enrollment/randomization
-00:20 rescue medication given if ongoing sz
-00:50 replicate standard care
-01:00 primary outcome assessment
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)
Recording Prospective Data: Primary & Back up

**Primary record**

Paper record produced by the clinical coordinator

Based on review of the chart, interviews with clinical care team.

However...coordinator could be late, team busy, shifts may change and there is potential for lost data

**Back up data recording device**

Elapsed Time:

60:06

60 Minutes

Please answer the following questions at 60 minutes from the infusion start.

Were there clinically apparent seizures?

- Yes
- No
- Unknown

Was responsiveness to verbal commands or noxious stimuli improved compared?

- Yes
- No
- Unknown

Submit Answers and Finalize
Safety Outcomes at T0 +60

• **Life-threatening hypotension:** Within 1 hour of start of infusion of the study drug, systolic blood pressure remains below specified levels on two consecutive readings at least 10 minutes apart and remains below specified levels for more than 10 minutes despite reduced drug infusion rate or its termination and a fluid challenge.
  - “Specified levels” for systolic blood pressure are 90 mmHg in adults and children older than 13 years old, 80 mmHg in children 7 to 12 years old, and 70 mmHg in children 2 to 6 years of age.

• **Life-threatening cardiac arrhythmia:** Any arrhythmia that occurs within 1 hour of start of infusion of the drug that persists despite reducing rate of drug infusion, or that requires termination with chest compressions, pacing, defibrillation, or use of an anti-arrhythmic agent or procedure.
Secondary Outcomes

- Occurrence of life threatening Hypotension or cardiac arrhythmia,
- 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
STUDY DESIGN
Primary Objective

• To determine the most effective and/or the least effective treatment of benzodiazepine-refractory status epilepticus (SE) among patients older than 2 years.

• Three active treatment arms:
  • fosphenytoin (FOS)
  • levetiracetam (LEV)
  • valproic acid (VPA)
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.
Study Design by Berry Consultants (Jason Connor, PhD)

- Bayesian Adaptive Design (extensive simulation study)
- Maximum sample size is N=795 total.
- Power of 90% when best has 65% response rate (vs 50% other arms)
- Primary endpoint at 60 minutes
- Followed until discharge/30 days
- Randomization will be stratified by three age groups
  - 2 - <18 years
  - 18-65 years
  - 66 years and older
Bayesian Adaptive Design Features

- Adaptively allocate to favor better treatments

- Drop poor performing arms
  - Relative to one another
  - Relative to 25% goal

- Stop early if we know the answer or know we won’t know
  - Efficacy stop if treatment clearly better
  - Futility stop if unlikely to ID a ‘best’ or ‘worst’
    - Do not stop if 1 worse and other 2 equally good
    - Futility stopping if all arms bad
Total No. of Subjects Enrolled

Fixed Randomization (Burn-in)  Adaptive Randomization (updated every 100 subjects)

Fos-phenytoin

Valproate

Levetiracetam

Red circles in columns indicate randomization probabilities

Blue arrows indicate updates that occur at every 100 subjects (about every 6 months). Details below describe the logic at each update. N = number enrolled.

Continue enrolling (next 100 subjects)

Is N \geq 400? No

Are they all the same?

Is the predicted prob of finding a winner or loser < 0.05?

No

Do none of them work?

Is the predicted probability < 0.05 that any agent has a response rate >25%?

No

Do we have a winner?

Is the predicted prob > 0.975 that any arm is the most effective?

No

Stop for futility

Yes

Stop for success

Yes

Adjust randomization probabilities (f_0, f_1, f_2)

If the randomization probability r_i for any arm is <0.05 then that arm stops enrollment for that update (r_i=0). If the allocation in a subsequent update is >0.05 the arm re-enters. If the Pr(response rate >25%) drops below 0.05 for any arm, the arm is permanently dropped from the study.
Adaptive Allocation

• Randomize N=300 patients equally
  • At N=300 begin adaptive allocation
  • Update allocation probability after every 100 subjects (N = 300, 400, ..., 700)

• Adaptive allocations after every 100 subjects equates to approx. every 6 months given expected accrual

• Adaptively allocate to
  • Favor better performing treatments
  • Favor treatments with greater uncertainty

$$r_t \propto \sqrt{Pr(p_t = \max(p)) \frac{Var(p_t)}{n_t}}$$

• If allocation probability ($r_t$) < 5%, suspend accrual
  • Allocation probability increased in remaining arms

• If $Pr(p_t \geq 0.25) < 0.05$, drop arm
Early Stopping

• Begins after **400 patients**
  • Evaluated after every additional 100 patients accrued to coincide with adaptive allocation assessments (i.e. N= 400, 500, 600, 700)

• Early Success Stopping:
  • If arm has 97.5% probability of having highest success rate
    • i.e. \( Pr(p_t = \text{max}(p)) \geq 0.975 \)

• Early Futility Stopping
  • If predicted probability of success (ID ‘winner’ or ‘loser’ at the max N=795) < 0.05
    • If all arms have been permanently dropped
      • i.e. \( \text{Pr}(p_t \geq 0.25) < 0.05 \) for all arms
SAMPLE TRIAL
1st Interim Analysis: N = 300 Subjects

Only Adaptive Allocation Allowed

<table>
<thead>
<tr>
<th>Look</th>
<th>N Enrolled</th>
<th>Observed Response Rate</th>
<th>Pr(Max Effective Trt)</th>
<th>Pr(Allocation)</th>
<th>Pred Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>LVT</td>
<td>fPHT</td>
<td>VPA</td>
<td>LVT</td>
<td>fPHT</td>
</tr>
<tr>
<td></td>
<td>51/100</td>
<td>55/100</td>
<td>64/100</td>
<td>0.025</td>
<td>0.092</td>
</tr>
</tbody>
</table>
### 2nd Interim Analysis: N = 400 Subjects

*Adaptive Allocation AND Early Stopping Allowed*

<table>
<thead>
<tr>
<th>Look</th>
<th>N Enrolled</th>
<th>Observed Response Rate</th>
<th>Pr(Max Effective Trt)</th>
<th>Pr(Allocation)</th>
<th>Pred Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVT</td>
<td>fPHT</td>
<td>VPA</td>
<td>LVT</td>
<td>fPHT</td>
</tr>
<tr>
<td>300</td>
<td>51/100</td>
<td>55/100</td>
<td>64/100</td>
<td>0.025</td>
<td>0.092</td>
</tr>
<tr>
<td>Next 100</td>
<td>6/11</td>
<td>19/26</td>
<td>39/63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>57/111</td>
<td>74/126</td>
<td>105/163</td>
<td>0.01</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- **N Enrolled**: Number of subjects enrolled at each look.
- **Observed Response Rate**: Percentage of subjects in each treatment group.
- **Pr(Max Effective Trt)**: Probability of selecting the most effective treatment.
- **Pr(Allocation)**: Probability of allocating subjects to each treatment group.
- **Pred Prob**: Predicted probability at each look.
**3rd Interim Analysis: N = 500 Subjects**

*Adaptive Allocation AND Early Stopping Allowed*

<table>
<thead>
<tr>
<th>Look</th>
<th>N Enrolled</th>
<th>Observed Response Rate</th>
<th>Pr(Max Effective Trt)</th>
<th>Pr(Allocation)</th>
<th>Pred Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>fPHT</td>
<td>VPA</td>
<td>LVT</td>
<td>fPHT</td>
</tr>
<tr>
<td></td>
<td>51/100</td>
<td>55/100</td>
<td>64/100</td>
<td>0.025</td>
<td>0.092</td>
</tr>
<tr>
<td>400</td>
<td>57/111</td>
<td>74/126</td>
<td>105/163</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Next</td>
<td>5/12</td>
<td>20/38</td>
<td>34/50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>42%</td>
<td>53%</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>62/123</td>
<td>94/164</td>
<td>139/213</td>
<td>0.004</td>
<td>0.056</td>
</tr>
</tbody>
</table>
## 4th Interim Analysis: N = 600 Subjects

**Adaptive Allocation AND Early Stopping Allowed**

<table>
<thead>
<tr>
<th>Look</th>
<th>N Enrolled</th>
<th>Observed Response Rate</th>
<th>Pr(Max Effective Trt)</th>
<th>Pr(Allocation)</th>
<th>Pred Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVT</td>
<td>fPHT</td>
<td>VPA</td>
<td>LVT</td>
<td>fPHT</td>
</tr>
<tr>
<td>300</td>
<td>51/100</td>
<td>55/100</td>
<td>64/100</td>
<td>0.025</td>
<td>0.092</td>
</tr>
<tr>
<td>400</td>
<td>57/111</td>
<td>74/126</td>
<td>105/163</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>500</td>
<td>62/123</td>
<td>94/164</td>
<td>139/213</td>
<td>0.004</td>
<td>0.056</td>
</tr>
<tr>
<td>Next</td>
<td>3/3</td>
<td>17/28</td>
<td>55/69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>100%</td>
<td>61%</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>65/126</td>
<td>111/192</td>
<td>194/282</td>
<td>0.000</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Trial stops early for identifying best treatment**
Final Analysis: N = 600 Subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observed</th>
<th>%</th>
<th>95% CI</th>
<th>Pr(Best)</th>
<th>Pr(Worst)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVT</td>
<td>65/126</td>
<td>51.6%</td>
<td>(.429, .601)</td>
<td>0.0005</td>
<td>0.862</td>
</tr>
<tr>
<td>fPHT</td>
<td>111/192</td>
<td>57.8%</td>
<td>(.507, .646)</td>
<td>0.007</td>
<td>0.138</td>
</tr>
<tr>
<td>VPA</td>
<td>194/282</td>
<td>68.8%</td>
<td>(.632, .739)</td>
<td>0.992</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Difference Observed 95% CI Pairwise Comparison

<table>
<thead>
<tr>
<th>Difference</th>
<th>Observed</th>
<th>95% CI</th>
<th>Pairwise Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA – fPHT</td>
<td>0.110</td>
<td>(0.022, 0.197)</td>
<td>Pr(VPA&gt;fPHT) = 0.993</td>
</tr>
<tr>
<td>VPA – LVT</td>
<td>0.172</td>
<td>(0.069, 0.272)</td>
<td>Pr(VPA&gt;LVT) &gt; 0.999</td>
</tr>
<tr>
<td>fPHT - LVT</td>
<td>0.062</td>
<td>(-0.049, 0.172)</td>
<td>Pr(fPHT&gt;LVT) = 0.862</td>
</tr>
</tbody>
</table>
ORGANIZATION AND CULTURE
Why

Simon Sinek
Start with Why
http://www.ted.com/talks/simon_sinek
Make people better
Organization

NINDS

Principal Investigators

SDMC  CCC  Pharm  Phenom

PECARN  NETT
Can’t tell the players without a program...

- **NINDS**  
  Brandy Fureman, Robin Conwit, Scott Janis

- **Prime (U Virginia)**  
  Jaideep Kapur, Amy Fansler, Emily Gray

- **CCC (Michigan)**  
  Robert Silbergleit, Valerie Stevenson, Erin Bengelink, Arthi Ramakrishnan, Deneil Harney, Joy Black

- **SDMC (S Carolina)**  
  Jordan Elm, Caitlin Ellerbe, Catherine Dillon, Cassidy Conner, Kristina Hill

- **PECARN**  
  Jim Chamberlain, Kate Shreve

- **Pharm (Minnesota)**  
  Jim Cloyd, Lisa Coles

- **Phenomenology**  
  Dan Lowenstein, Shlomo Shinnar
Prime – University of Virginia

• Overall Grant Management
• Organize and Direct Leadership
• FDA and IND Sponsorship
• Publications
CCC

- Management of protocol and MoP
- Site Monitoring
- Internal safety review
- EFIC oversight
- Regulatory management
- Adjudication core support
- Protocol assist device data collection
SDMC

• Biostatistical support and study design
• Randomization programming (RAR)
• Data management and validation
• CTMS WebDCU (data, regulatory, site management, invoicing, drug tracking)
• DSMB Report generation
• Publication support
Pharmacology Core

- Pharmacology core oversees acquisition, manufacturing and testing of drugs.
- Assist with preparing and maintaining IND
- Manufacturing facility: UC Davis GMP facility
- Testing UC Davis facility and Analytical Research Laboratories, Oklahoma

Pharmacology core team members:
- Minnesota - Jim Cloyd, Lisa Coles
- UC Davis – Gerhard Bauer, Brian Fury
- ARL – Jessica Munson
Phenomenology Core

• The Core will monitor the consistency of primary outcomes determined locally.

• Adjudicate secondary outcomes.

• Adjudication Core Members – Dan Lowenstein, Shlomo Shinnar, Hannah Cock, Nathan Fountain
Quality

- Quality by Design
- Focused efforts on “errors that matter”
Monitoring

- Central Data Monitoring
- Source Document Verification (Site and Remote)
- Risk-based Allocation
- Site Monitoring
Performance

- Enrollment
- Deviations
- Timeliness
- Compliance
Culture

- Electronic platforms
- Transparency
- Research on Research
- Ancillary studies
ESETT 2 Year Timeline

Drug testing: 11/15/2014 - 2/15/2015
IND review: 3/1/2015 - 4/1/2015
EFIC activities: 4/1/2015 - 8/1/2016
IRB review: 4/1/2015 - 8/12/2016
App Development: 4/1/2015 - 8/1/2015
Site prep incl investigator mtg: 9/1/2015 - 2/15/2016
Subcontracts executed: 01/2014 - 12/31/2015
Operationalize phenomenology core: 4/1/2015 - 9/1/2015

Drug testing complete: 2/15/2015
IND review complete and study cleared: 4/30/2015
EFIC activities complete at 2 sites: 9/1/2015
2 patients enrolled: 9/30/2015
100 patients enrolled: 9/30/2016

9/30/2015: 2 patients enrolled
9/1/2015: IRB review complete and enrollment commences
2/15/2015: Drug testing complete
4/30/2015: IND review complete and study cleared
4/1/2015 - 8/1/2016: EFIC activities complete at 2 sites
4/1/2015 - 8/12/2016: IRB review complete at 2 sites & enrollment commences