A clinical trial of three anticonvulsant medications for status epilepticus

The Established Status Epilepticus Treatment Trial (ESETT)

Study Protocol and Statistical Analysis Plan

This supplement contains the following items:

1. Original protocol, final protocol, and a summary of changes (embedded at the front of the final protocol).

2. Original statistical analysis plan, final statistical analysis plan, summary of changes for all versions (embedded at the front of the final statistical analysis plan), and the appendix for the statistical analysis plan.

STUDY PROTOCOL

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.

Study Chair: Jaideep Kapur, MD, Professor, University of Virginia

Supported by: The National Institute of Neurological Disorders and Stroke (NINDS)
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ClinicalTrials.gov ID: NCT01960075

Sponsor of IND: Jaideep Kapur, IND 119,756

Version: 1
22 December 2014

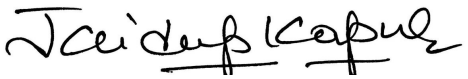
adapted for the NETT from the NIND phase III template at:
http://www.ninds.nih.gov/research/clinical_research/toolkit/protocoltemplate.htm

PROTOCOL CHANGES

If amended versions of this protocol are required, this page will be populated with a specific log of all changes.

PROTOCOL SIGNATURE PAGE

I have read the attached clinical protocol titled Established Status Epilepticus Treatment Trial (ESETT) Version 1, dated 22 December 2014. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.



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Sponsor's Signature Date of Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described.

I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make all reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

_____

Investigator's Signature Date of Signature

CONTACT INFORMATION

For updated contact information, including the Emergency 24/7 Toll Free Contact Number, please refer to the study website ESETT.org or the study Manual of Procedures.

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TABLE OF ABBREVIATIONS

AE	Adverse Event
CCC	Clinical Coordinating Center
cEEG	Continuous Electroencephalogram Monitoring
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events Version 3.0
DCR	Data Clarification Request
DCU	Data Coordination Unit
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
ECG	Electrocardiogram
EEG	Electroencephalogram
EFIC	Exception from Informed Consent
EMS	Emergency Medical Services
ESE	Established Status Epilepticus
ESETT	Established Status Epilepticus Treatment Trial
ET	Endotracheal
FDA	Food and Drug Administration
FOS	Fosphenytoin
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IM	Intramuscular
IND	Investigational New Drug
IO	Intraosseous
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LEV	Levetiracetam
mg	Milligram
Min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
MoP	Manual of Procedures
MM	Medical Safety Monitor
MUSC	Medical University of South Carolina
NETT	Neurological Emergencies Treatment Trials
NINDS	National Institute of Neurological Disorders and Stroke

PECARN	Pediatric Emergency Care Applied Research Network
PGS	Purple Glove Syndrome
PHT	Phenytoin
PHTSE	Pre-hospital Treatment of Status Epilepticus Trial
PI	Principal Investigator
PR	Per Rectum
RAMPART	Rapid Anticonvulsant Medication Prior to Arrival Trial
RAR	Response Adaptive Randomization
RASS	Richmond Agitation and Sedation Score
RBC	Red Blood Cell
SAE	Serious Adverse Event
SDMC	Statistical & Data Management Center
SE	Status Epilepticus
SSL	Secure Socket Layer
SOP	Standard Operating Procedures
VAL	Valproic acid
WebDCU	Web-based Clinical Trial Management System

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SYNOPSIS

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.

Objectives: 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). The **second** objective is comparison of three drugs with respect to secondary outcomes. The final objective is to ensure that the trial is informative for treatment of established SE in children by describing the effectiveness, safety, and rate of adverse reactions of these drugs in children.

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. The following are **secondary outcomes**: occurrence of life threatening hypotension or cardiac arrhythmia, time to termination of seizures, intubation, admission to ICU, seizure recurrence, length of stay in the ICU and hospital, mortality, and Richmond agitation and sedation score at 60 minutes, will be compared between treatment groups.

Methods: This is a randomized, multicenter, Bayesian response adaptive comparative effectiveness trial of three active treatments in patients with status epilepticus who have failed treatment with benzodiazepines. Each subject will be followed until discharge or 30 days from enrollment, whichever comes first. This trial will be monitored for early success and futility.

Inclusion: Patients greater than or equal to 2 years of age, witnessed to have a clinically apparent seizure in the ED, 5-30 minutes after already having received at least an adequate dose of benzodiazepines for generalized, tonic-clonic convulsion(s). Adequate doses of benzodiazepines for this study are defined as: diazepam 10 mg IV, lorazepam 4 mg IV, or midazolam 10 mg IV or IM for subjects greater than or equal to 40 kg, and diazepam 0.3mg/kg IV, lorazepam 0.1 mg/kg IV or midazolam 0.3mg/kg IM or 0.2 mg/kg IV for subjects less than 40 kg. These drugs may have been administered in two or more divided doses, including in the out-of-hospital setting.

Interventions and Duration: The required concentrations of the study drugs (FOS 16.66 mg/ml, VPA 33.33 mg/ml and LEV 50 mg/ml) will be produced, packaged and labeled by the University of California at Davis Good Manufacturing Practice (GMP) facility and shipped to the study sites. The study drugs are identical in appearance, formulation, packaging, and administration

(including volume and rate of infusion). The assigned treatment dose (FOS 20 mg/kg, LEV 60 mg/kg or VPA 40 mg/kg) will be infused over 10 minutes. The study participants will be observed for 20 minutes, while the duration of clinical seizures and response to verbal or painful stimuli is recorded. At 60 minutes from start of study drug infusion, the primary outcome is determined.

Randomization: Any patient witnessed to have seizures in the emergency department (ED) will be evaluated for enrollment based on inclusion and exclusion criteria. Enrollment will occur under exception from informed consent rules (EFIC) due to the emergent and life-threatening nature of SE. This is an intent-to-treat study so all subjects randomized will be included in the primary analysis. Time of randomization is the time when the infusion pump, connected to study drug vial and patient's IV catheter, is switched on. The randomization scheme will be equal allocation (1:1:1) for the first 300 patients. Once 300 subjects are randomized, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm.

Interim Analyses: Interim monitoring for success and futility will begin after 400 subjects have been enrolled and will be repeated after every additional 100 subjects are enrolled . This trial will stop early for success if the analysis identifies the maximum effective treatment with at least 97.5% probability.

Sample Size: This study will randomize a maximum target of 795 subjects over 4 years, at an accrual rate of approximately 16.5 subjects per month. This sample size provides approximately 90% power to identify the most effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (an absolute difference of 15%). A 15% difference is the minimum clinically important difference sufficient to change clinical practice. The trial operating characteristics for this adaptive design were determined via an extensive simulation study, which ensures the type I error probability is less than 0.05 under a variety of scenarios.[37]

Participating Sites: Patients will be recruited by two national emergency research networks: Neurological Emergencies Treatment Trials (NETT) network and Pediatric Emergency Care Applied Research Network (PECARN). Each network has successfully participated in SE treatment trials in compliance with EFIC regulations.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to determine the most effective and/or the least effective treatment (between fosphenytoin, levetiracetam and valproic acid) of benzodiazepine-refractory SE among patients greater than or equal to 2 years. 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.

1.2 Secondary Objectives

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

2. BACKGROUND

2.1 Rationale

SE is defined as a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness between seizures (Lowenstein 1999). Epidemiological studies carried out in Richmond, VA, found an annual incidence of SE ranging from 41/100,000-61/100,000 (DeLorenzo 1996). Based on these studies, there are approximately 120,000-180,000 episodes of convulsive SE each year in the US. SE affects individuals of all ages from the very young to the elderly. It complicates many neurological and systemic illnesses. The mortality associated with SE is estimated as 17%. SE also leads to morbidity including cognitive defects and neurological injury. The morbidity and mortality of SE is determined by the underlying cause of the SE and the length of time in SE (Neligan 2010; Towne 1994). The Febrile status epilepticus study (FEBSTAT) suggests that SE, but not individual seizures, injures the hippocampus (Nordli, 2012; Shinnar 2012). Early termination of SE can limit development of refractory SE, neurological injury and mortality in experimental animals (Fujikawa 2005; Kapur 1997). SE is particularly common in children (Shinnar . 1997). Although multiple different etiologies such as infection, tumors, fever, preexisting neurological injury or brain malformation cause SE, the primary goal of treatment is prompt termination of seizures because adverse consequences of SE increase with seizure duration (Chen 2007; Lothman 1990; Meldrum 1973; Meldrum 1986).

SE is initially treated with benzodiazepines. This selection is based on three double-blind, randomized, controlled clinical trials (Alldredge 2001; Treiman 1998, SIlbergleit 2012). In the VA Cooperative Study (Treiman 1998), intravenous lorazepam was found to be superior to phenytoin. In the Pre-hospital Treatment of Status Epilepticus (PHTSE) study (Alldredge 2001), lorazepam and diazepam were found to be superior to placebo. In these studies, lorazepam was effective in terminating SE in 55-65% of patients. The recently published RAMPART study compared intramuscular midazolam to intravenous lorazepam for the initial treatment of SE (Silbergleit 2012). It concluded that intramuscular midazolam is at least as safe and effective as intravenous lorazepam for patients in convulsive status epilepticus (Silbergleit 2012). Benzodiazepines are also the first treatment of choice in children (Loddenkemper 2011). The recently published Pediatric Seizure Study found that lorazepam was not superior to diazepam for pediatric SE (Chamberlain 2014). Unfortunately, approximately 35-45% of patients are refractory to benzodiazepines. Benzodiazepine-refractory SE is also called established SE. ESETT is a clinical trial testing the relative efficacy and safety of three treatments in patients who do not respond to benzodiazepine treatment (Cock 2011; Prasad 2005). The need for such a trial has been emphasized in review articles, guidelines and by experts in the field (Lowenstein 2005;Meierkord 2010; Wheless 2008).

For the purpose of this trial, “established SE (ESE)” is defined as an episode of generalized convulsive SE in which seizure activity continues despite administration of adequate doses of

benzodiazepines. It has long been recognized that SE is a dynamic and rapidly evolving condition which eventually becomes self-sustaining (Lothman 1990; Lothman 1989; Treiman 1990; VanLandingham 1991a; VanLandingham 1991b). Ongoing seizures rapidly modify neuronal activity and synaptic function (Chen 2007; Macdonald 1999). This rapid neuronal plasticity is manifested in changes in seizure behavior, EEG patterns, sensitivity to drugs, and evolution of neuronal injury and death. EEGs recorded from patients soon after onset of generalized convulsive SE demonstrate discrete seizures interspersed with normal activity, which evolves to continuous waxing and waning spike–wave discharges (Treiman 1990). Benzodiazepines given soon after the onset of generalized convulsive status epilepticus are effective in terminating seizures in 60-72% of patients. As time passes, these drugs become far less effective, terminating seizures in less than 25% of patients (Treiman 1998).

Benzodiazepines act on GABA-A receptors and enhance inhibitory synaptic transmission (Goodkin 2009). In experimental animals, benzodiazepines terminate seizures effectively if they are given soon after the start of seizures--when EEG demonstrates recurrent seizures and behavioral seizures are mild. Benzodiazepines are less effective in treating longer lasting SE, especially after electrographic seizures have merged and 10 or more minutes have elapsed since first generalized tonic-clonic seizure (Jones 2002; Kapur 1997; Walton 1988; Wang 2009). Studies further reveal that inhibitory synaptic transmission mediated by GABA-A receptors is reduced in the hippocampi of animals in ESE (Goodkin 2008; Kapur 1995; Kapur 1997; Naylor 2005; Terunuma 2008). Biochemical studies reveal a decrease in the number of functional receptors on the post-synaptic membrane in the hippocampi of animals in established SE (Goodkin 2005; Goodkin 2008; Naylor 2005; Terunuma 2008). This rapid receptor plasticity is believed to be mediated by prolonged seizures, which activate many second messenger pathways (Brunig 2001; Pal 2001). In summary, prolonged seizures modify GABA-A receptors and lead to ESE.

Further treatment should ideally focus on mechanisms other than GABA-A receptors, such as sodium channels, calcium channels, or glutamatergic transmission. Currently, there are several drugs available in the intravenous formulation that can modify these systems. Lacosamide and FOS modify sodium channels. LEV modifies glutamatergic synaptic transmission by binding to the synaptic vesicle proteins. VPA has multiple actions on several neurotransmitter systems and ion channels. These mechanisms are described in the respective package inserts.

2.2 Study Drugs

The primary goal of treatment of ESE is to terminate seizures rapidly, without causing respiratory or cardiovascular compromise, or coma. The active form of the drug must enter the brain rapidly, access its target and stop ESE. Three drugs were selected for this study based on

current recommendations of professional groups, current clinical practice, and safety and efficacy data.

Recently, the Status Epilepticus Guideline Writing Committee of the Neurocritical Care Society (NCS) reviewed current evidence and classified it according to American Heart Association/American College of Cardiology guidelines for evidence rating (Brophy 2012). The Neurocritical Care Society rated common anticonvulsants for the treatment of SE as follows:

VPA: Class IIa, level A—weight of evidence/opinion is in favor of usefulness/efficacy based on data derived from multiple randomized clinical trials.

FOS: Class IIa, level B--weight of evidence/opinion is in favor of usefulness/efficacy based on data derived from a single randomized trial or nonrandomized trials.

LEV: Class IIb, level C--weight of evidence/opinion is in favor of usefulness/efficacy based on consensus opinion of experts.

These three medications are sometimes referred to by certain brand names. Fosphenytoin may referred to as Cerebyx or, inaccurately, as Dilantin, the brand name of the active metabolite of this pro-drug. Levetiracetam may be referred to as Keppra. Valproic acid may be referred to as Depacon or Depakote.

The NCS guidelines recommended use of either FOS or VPA for the treatment of established SE (Brophy 2012).

To identify current practice, a critical care pharmacy group studied the patterns of anticonvulsant use for benzodiazepine refractory status epilepticus in the neurocritical care units. This survey analyzed the medical records of 10-20 recent SE patients from the critical care units at 15 academic medical centers. Among the 150 patients studied, benzodiazepines were the most commonly used first agent (75%) for treatment of SE. FOS was the most commonly used second anticonvulsant (33%). LEV was less commonly used (10%) and VPA was rarely used (<2 %) (Cook 2012). The NCS Status Epilepticus Guideline Writing Committee reported the preferences of 50 identified experts among neurointensivists, neurologists and epileptologists for the treatment of ESE. Among the respondents for this survey, 80% chose FOS (or phenytoin), 6% chose LEV and 2% chose VPA (Riviello 2006). In a survey of 21 pediatric ED directors from the Pediatric Emergency Care Applied Research Network (PECARN), FOS was the most commonly used treatment for ESE in pediatric patients followed by LEV, phenobarbital, and VPA.

Intravenous formulations are available for FOS, LEV, VPA, lacosamide and phenobarbital. Of these drugs, phenobarbital causes sedation and respiratory depression, especially in those who have been treated with benzodiazepines. This side effect limits the popularity of phenobarbital

as a second line agent for SE. The safety of rapid intravenous administration of lacosamide has been established in adults but not in children (Fountain 2012). Children constitute a large fraction of patients with SE. Three hundred thirty-six of approximately 795 of subjects to be randomized into this study will be children. There are limited data on the efficacy of lacosamide in established SE, especially in children. For these reasons, lacosamide and phenobarbital were not included in the study.

2.3 FOS (fosphenytoin)

FOS is the most commonly recommended treatment for ESE in many current treatment guidelines (Brophy 2012; Loddenkemper 2011; Meierkord 2010) and is generally considered the standard of care. In a survey of critical care neurologists published in 2003, 95% of responders (n= 106) used FOS or phenytoin for the treatment of ESE (Claassen 2003). Two more recent surveys suggest that it is currently the most commonly used drug for the treatment of ESE in the US (Cook 2012; Riviello 2012). A survey of pediatric ED physicians belonging to the Pediatric Emergency Care Action Research Network (PECARN) reported that the majority of physicians treating children use FOS for the treatment of ESE.

Pharmacokinetics, dose and rate of administration: In order to achieve rapid termination of seizures, drugs need to be administered rapidly. Drugs are delivered over a 10 minute infusion period in ESETT. FOS can be administered at a maximum rate of 150 mg/min in order to avoid hypotension and cardiac arrhythmias (see boxed warning, package insert). This limits the maximum dose of the drug that can be administered safely over 10 minutes to 1500 mg. The recommended loading dose of FOS is 18-20 mg/kg. Therefore, patients weighing less than 75 kg will receive a loading dose 20 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 1500 mg over 10 minutes. Because more than 65% of adult men and 45% of adult women weigh more than 75 kg, weight-based dosing will typically apply to children and fixed dosing to adults. This dosing regimen is consistent with current recommendation for the use of anticonvulsants, where children are dosed on a mg/kg basis while adults are given fixed doses (see package insert phenytoin, LEV, and VPA). In general, children are given larger doses of anticonvulsants because of differences in the pharmacokinetics.

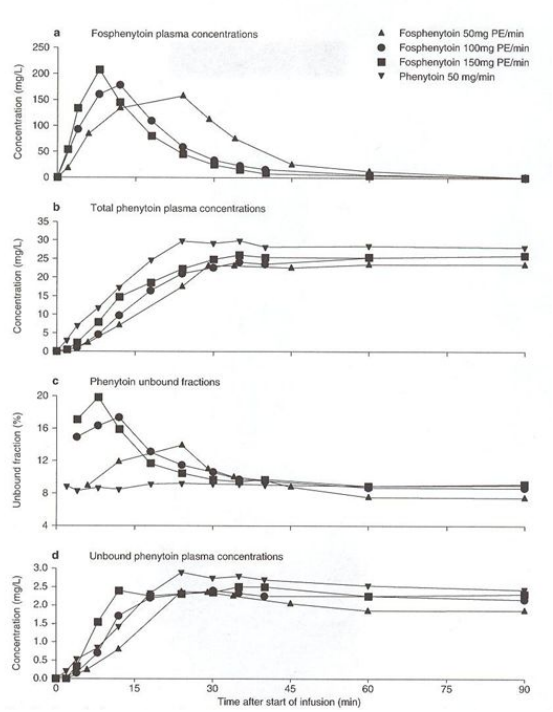

Figure 1. (Fischer 2003)

The pharmacokinetics of FOS (1200 mg) administered at the rate of 150 mg phenytoin equivalents (PE)/min is illustrated in Figure 1 (Fischer 2003). Most clinically relevant is panel d showing unbound (free) phenytoin plasma concentrations following administration. These remain in 2.0- 3.0 mg/L range 90 minutes after administration. The accepted therapeutic range of unbound plasma concentration is 1 to 2 mg/L. Patients receiving a single dose of FOS (1500 mg) are expected to maintain a free phenytoin concentration above 2 mg/L for 90 to 120 minutes. It is thus reasonable in the patient who has stopped seizing to wait for 2 hours from start of infusion to start or restart anticonvulsant medication.

FOS is a prodrug which must be converted to phenytoin (PHT) to exert its action (Walton 1990). FOS has to undergo dephosphorylation before it can enter the brain. Figure 2 illustrates the rate of accumulation of PHT in rat plasma and brain after single intraperitoneal injection of FOS (called ACC 9653 at the time of publication) or PHT (Walton 1990). Note that peak plasma PHT concentration was achieved 30 minutes after FOS injection. The peak brain PHT level was attained 60 minutes after administration. PHT is effective against partial onset seizures and secondarily generalized seizures, but its efficacy in primary generalized seizures is not established. It exerts its anticonvulsant action by stabilizing the inactivated state of sodium channels (Macdonald 1994). FOS gets converted into phenytoin and enters the brain. FOS can be administered faster than phenytoin.

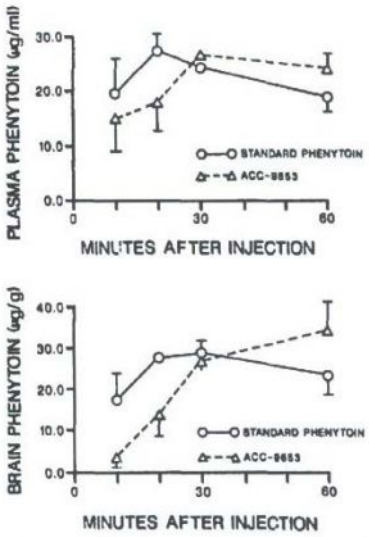

Fig. 1. Phenytoin concentrations in plasma (upper figure) and brain (lower figure) following i.p. injection of 130 mg/kg ACC-9653 or 120 mg/kg standard phenytoin. Each point is the mean ± standard error for 3 rats.

Figure 2. (Walton 1990)

Safety: According to the package insert, the dose of IV FOS (15 to 20 mg PE/kg) that is used to treat status epilepticus is administered at a maximum rate of 150 mg PE/min to avoid cardiovascular side effects. Hypotension may occur, especially after IV administration at high doses and high rates of administration. Severe cardiovascular reactions and fatalities, such as atrial and ventricular conduction depression and ventricular fibrillation, have been reported following PHT administration, especially in elderly or gravely ill patients. These complications are less frequent with FOS, but careful cardiac monitoring is still needed when administering IV loading doses of FOS. Reduction in rate of administration or discontinuation of dosing may be necessary. This ESETT protocol calls for these reductions if needed while administering the study drug.

Rash: Exfoliative, purpuric, or bullous, rashes, Stevens-Johnson syndrome, or toxic epidermal necrolysis are known to occur with chronic administration of PHT.

Hepatotoxicity: Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes.

Hemopoietic system: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and

pancytopenia with or without bone marrow suppression have been reported.

Prenatal exposure to phenytoin was not found to have additional significant clinical risk in a recent Cochrane meta-analysis (Bromley 2014). Theoretical risks are related to prolonged exposures rather than single dose exposures as in this trial. Theoretical risks include congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. Patients known to be pregnant will be excluded from this trial anyway as per the secretarial waiver allowing studies with EFIC.

Efficacy in animal studies: Fosphenytoin and PHT are not effective in termination of benzodiazepine refractory SE in animal model ESE. In an electrical stimulation model where excitatory inputs to the hippocampus were stimulated (perforant path) for 60 minutes, the resulting in-animal model ESE was not terminated by phenytoin (50 mg/kg) given intravenously (Mazarati 1998). In another animal model of ESE based on electrical stimulation of the hippocampus for 90 minutes, phenytoin did not suppress seizures (Prasad 2002). Finally, in a cholinergic stimulation (nerve agent-induced) animal model ESE, FOS had little or no therapeutic effect either administered alone or in combination with diazepam (McDonough 2004).

Efficacy in open studies: In open-label studies for initial treatment of SE, the reported efficacy of PHT in terminating SE ranges from 44-88% (Trinka 2009). In the VA Cooperative study (Treiman 1998), PHT was effective in initial treatment of convulsive SE in 42% of patients, but in only 7.7 % patients with subtle SE. Effectiveness in ESE was not studied. A systematic, retrospective analysis concluded that phenytoin was effective in 58.6% of patients with SE who did not respond to benzodiazepines (Alvarez 2011).

2.4 LEV (levetiracetam)

Recently published guidelines for the treatment of ESE in adults and children recommend LEV as an alternative to FOS (Brophy 2012; Loddenkemper 2011; Meierkord 2010). In surveys of experts and pediatric ED physicians, LEV is the second most commonly used drug for the treatment of ESE in neurological intensive care units (Cook 2012; Riviello 2012). It is used for the treatment of partial and generalized tonic-clonic seizures, myoclonic seizures and seizures associated with juvenile myoclonic epilepsy. It binds to synaptic vesicle protein 2 (SV2) and modulates neurotransmission. An intravenous formulation of the drug has been available for several years and it is labelled for use when patients cannot swallow or for initiating therapy for

seizure.

Pharmacokinetics & safety: Doheny et al investigated the plasma and brain concentrations of LEV after bolus intraperitoneal injection of 20, 40 or 80 mg/kg of the drug to rats. Serum LEV concentration increases and peaks rapidly, but brain accumulation is slow and peaks 90-100 minutes after administration (Doheny 1999).

Dose and rate of administration: The recommended LEV dose in children up to 40 kg is 20-60 mg/kg per day (package insert). In adults, the recommended dose range is 1-3 g per day, but higher doses up to 6 g per day are commonly used. The safety of rapid intravenous administration of LEV has been assessed. Intravenous doses of 2500 mg have been administered over 5 minutes and doses of 4000 mg have been given over 15 minutes safely in adults (Ramael 2006a). The common adverse effects in these patients were dizziness, somnolence, irritability and headache (Ramael 2006a). Based on these considerations, subjects weighing up to 75 kg will receive a loading dose 60 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 4500 mg over 10 minutes.

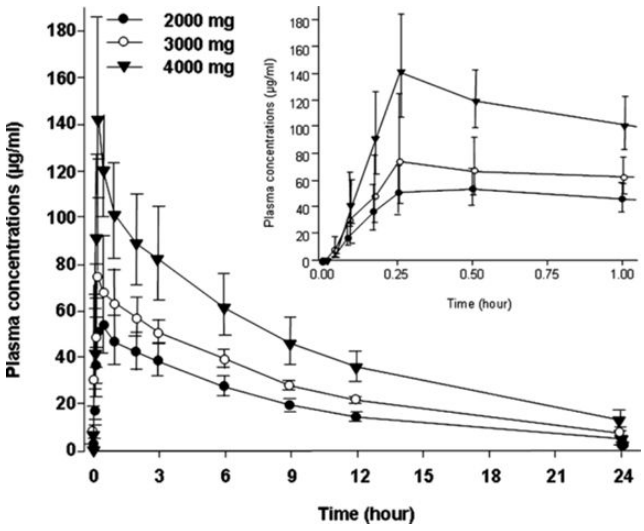

Figure 3. (Ramael 2006b)

Figure 3 demonstrates the pharmacokinetics of LEV following injection of 2000, 3000 or 4000 mg of the drug (Ramael 2006b). It is noteworthy that within 15 minutes of injection the plasma concentration of LEV peaks and remains above 40 µg /ml for 9 hours. The therapeutic concentration of LEV is considered to be 12 to 46 µg /ml. Therefore, patients treated with LEV are likely to have therapeutic concentrations of the drug for 8 to 10 hours after the start of infusion.

Safety: Suicidal ideation: Chronic administration of LEV increases the risk of suicidal thoughts or behavior. Patients treated with LEV for should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Risk of suicidal ideation associated with a single dose of LEV is unknown.

CNS: CNS effects include somnolence and fatigue, coordination difficulties, and behavioral abnormalities observed in pediatric and adult population.

Hematopoietic: Minor, but statistically significant, decreases in total mean RBC count (0.03 x 106/mm3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in LEV-treated adult and pediatric patients in placebo-controlled trials.

Pregnancy Risks: The best available evidence is that there are no risks related to pregnancy from the administration of levetiracetam in humans. Current data suggests that the overall risk of major malformation after first trimester exposure to levetiracetam is within the population baseline risk of 1-3%, with no apparent adverse effects on long term child development. The effect of a single dose of LEV has not been studied, but would be of lower risk than repeated dosing (Chaudhry SA, 2014, Bromley 2014).

Efficacy in animal model ESE: LEV administered alone reduced the duration of perforant path stimulation–induced animal ESE (Mazarati 2004). When used in combination with diazepam, low doses of LEV rapidly terminated behavioral and EEG seizures (Mazarati 2004). In the cholinergic stimulation animal model of ESE, LEV administered alone suppressed behavioral seizures, but EEG seizures continued unabated (Zheng 2010).

Efficacy in open studies: Although no randomized controlled clinical trial for this agent has been performed, a large number of open case series and reports have been published. An analysis of publications until 2009 reported that 707 patients with various forms of SE had been treated with LEV. The success rate was about 70% (Trinka 2011). In ESE, the efficacy of LEV is reported as 51.7 % in one study (Alvarez 2011) and 73.2% in another study (Tripathi 2010).

2.5 VPA (valproic acid)

VPA was recommended for the treatment of ESE in recent guidelines (Brophy 2012; Meierkord 2010). In surveys, VPA is the third or 4th most commonly used drug for the treatment of ESE in the U.S. (Cook 2012; Riviello 2012). VPA is an anticonvulsant commonly used for the treatment of primary generalized seizures, myoclonic seizures and focal seizures. The drug has multiple actions on the GABA neurotransmitter system and calcium channels (Macdonald 1995). Valproate sodium is the salt of the valproate ion which is synonymous with VPA.

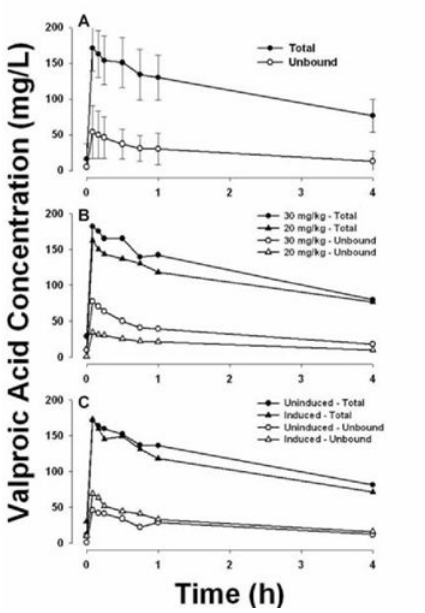

Figure 4. (Limdi 2007)

Pharmacokinetics: Subjects weighing up to 75 kg will receive a loading dose of 40 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 3000 mg over 10 minutes. Based on published pharmacokinetic data (Limdi 2007), serum VPA levels will peak between 150-200 mg/L within minutes of administration and then remain in the 50-150 mg/L range for the next 4 hours (see Figure 4). Pharmacokinetics of IV VPA has been studied in children with epilepsy (Birnbaum 2003; Panomvana Na 2006; Ramsay 2003; Visudtibhan 2011; Williams 2012). Recent studies suggest that the pharmacokinetics of rapid intravenously administered VPA conforms to models developed using oral VPA in children and oral and intravenous VPA in adults (Williams 2012). Intravenous VPA is safe in acutely ill children with recurrent seizures and in those with epilepsy (Birnbaum 2003; Ramsay 2003).

Dose and rate of administration: Recommended VPA dose ranges from 15-45 mg/kg/day. VPA has been administered rapidly by the intravenous route. In one study it was administered at the rate of up to 10 mg/kg/minute for doses up to 30 mg/kg (Limdi 2005). In another study in children it was given at rates up to 11 mg/kg/min for dose up to 40 mg/kg (Venkataraman 1999; Wheless 2004). The most common adverse events were injection site pain, pain with infusion, dizziness, and somnolence. Based on these considerations, subjects weighing up to 75 kg will receive a loading dose of 40 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 3000 mg over 10 minutes.

Safety in pregnant women Children born to mothers taking long durations of high doses of VPA during pregnancy may have a higher than expected incidence of reduced cognitive performance at ages 3 and 4.5 (McVearry 2009; Meador 2009; Werler 2011). These risks are dose dependent and vary across studies. They have only been found to be are associated with chronic administration of VPA (Bromley 2014). There is no evidence that a single dose of VPA

given during pregnancy can cause birth defects.

In a series of reviews of hepatotoxicity associated with VPA, Dreifuss and colleagues concluded that the primary risk of fatal hepatic dysfunction (1/500) was found in children 0 to 2 years old receiving VPA as polytherapy. The risk declined with age and was low in patients receiving VPA as monotherapy (1/37,000). No hepatic fatalities occurred in patients above the age of 10 years receiving VPA as monotherapy (Bryant 1996; Dreifuss 1987; Dreifuss 1989). There are reports that polymerase c gene (POLG) determines the risk of VPA -induced hepatotoxicity (Stewart 2010). However, the POLG polymorphisms were discovered in patients who had been chronically treated with VPA and had elevated hepatic enzymes. The authors concluded that the genetic variants reduced the regenerative capacity of the hepatocytes following injury. Patients with mutations in POLG have metabolic encephalopathy. There is no report of hepatotoxicity associated with a single dose of VPA. Patients below age 2, and those with known or suspected metabolic encephalopathy are excluded from ESETT.

Exclusion of patients known to be pregnant, younger than 2 years and with known or suspected metabolic encephalopathy will reduce the possibility of VPA exposure to the population at risk for toxicity. There is a small risk that a pregnant patient who is not identified as pregnant by history or physical examination will be included in the study. The risk of toxicity is mitigated by the fact that a single dose of VPA will be used. This risk should be weighed against the known morbidity and mortality of ESE and compared to the risk of administering FOS.

Clinical studies: VPA has been used for the treatment of SE in prospective or retrospective series and two randomized open trials (Trinka 2009). An analysis of these trials reported that 693 adults or children in SE have been treated with VPA and the response rate ranging from 60-83% of patients. A pilot prospective randomized open study reported a trend towards superiority of VPA to phenytoin in treatment of SE (Misra 2006). Another study reported that VPA controlled SE refractory to PHT (Agarwal 2007).

2.6 Systematic comparison of FOS, VPA, and LEV for the treatment of ESE

There is one systematic study of treatment of ESE (Alvarez 2011). In a retrospective analysis of protocol-driven treatment of ESE, 279 adult episodes of SE were identified prospectively in which either PHT or VPA or LEV was given in a non-randomized un-blinded fashion after benzodiazepines failed (labeled Alvarez in figure 5 below). VPA failed to control SE in 25.4%, PHT in 41.4% and LEV in 48.3% of episodes. Because patients were not balanced with regards to etiology and severity of SE, a post-hoc adjustment for severity and etiology was performed. After this adjustment the authors reported that LEV failed more often than VPA (Odds ratio (OR) 2.69: 95% confidence interval 1.16-6.08)). PHT was not significantly different from the other two compounds. The authors concluded that LEV is less effective than VPA for control of

ESE and called for a prospective randomized trial of these agents.

Two ESE treatment studies were open-label, randomized, prospective studies. In the first study (labeled Agarwal on figure 5), one hundred patients aged two or older who had failed IV diazepam were randomized to either 20 mg/kg of VPA or 20 mg/kg of PHT. SE was controlled in 44 (88%) patients treated with VPA and 42 (81%) patients treated with PHT (Agarwal 2007). No significant difference was found between VPA and PHT in this open-labeled study. In the second study (Tripathi 2010) patients were randomized to IV LEV or IV VPA after failing diazepam treatment of SE. Status epilepticus was terminated by IV LEV in 30 patients and by IV VPA in 28 patients. In this study as well, there was no significant difference between LEV and VPA. In summary, one large head-to-head comparison of these three agents raised the possibility that VPA is superior to LEV for the treatment of ESE. The other studies were inconclusive. Expert evaluation of the published data suggests that VPA (Class IIa level A) may be superior to FOS (Class IIa level B), which may be superior to LEV (class IIb level C).

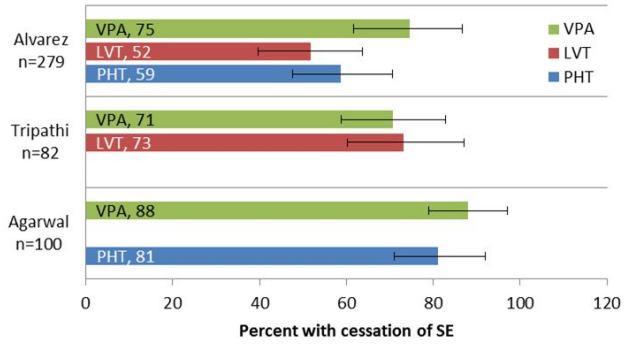

Figure 5. (Agarwal 2007, Alvarez 2011, Tripathi 2010)

In summary, current practice is to treat ESE with FOS or LEV. However no randomized controlled trials have demonstrated their efficacy in terminating ESE. Non-randomized and pilot studies suggest VPA may be more efficacious than LEV. Most expert ED physicians, neurologists, neuro-intensivists and pediatric neurologists believe that the next logical step is a randomized, blinded comparative efficacy study to decide the best treatment for ESE (Brophy 2012; Cock 2011; Loddenkemper 2011; Shorvon 2011; Trinka 2009).

3. STUDY DESIGN

This is a multicenter, randomized, Bayesian response-adaptive comparative effectiveness trial of three active treatments in patients with established SE who have failed treatment with benzodiazepines. Subjects will initially be randomized in a 1:1:1 ratio. Once 300 subjects are randomized, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm. Interim analyses are planned after 400, 500, 600, and 700 subjects are enrolled. At each interim analysis, there may be updates to the randomization probabilities. At each interim analysis, the trial may stop early for success or futility. The maximum approximate sample size is 795 subjects total.

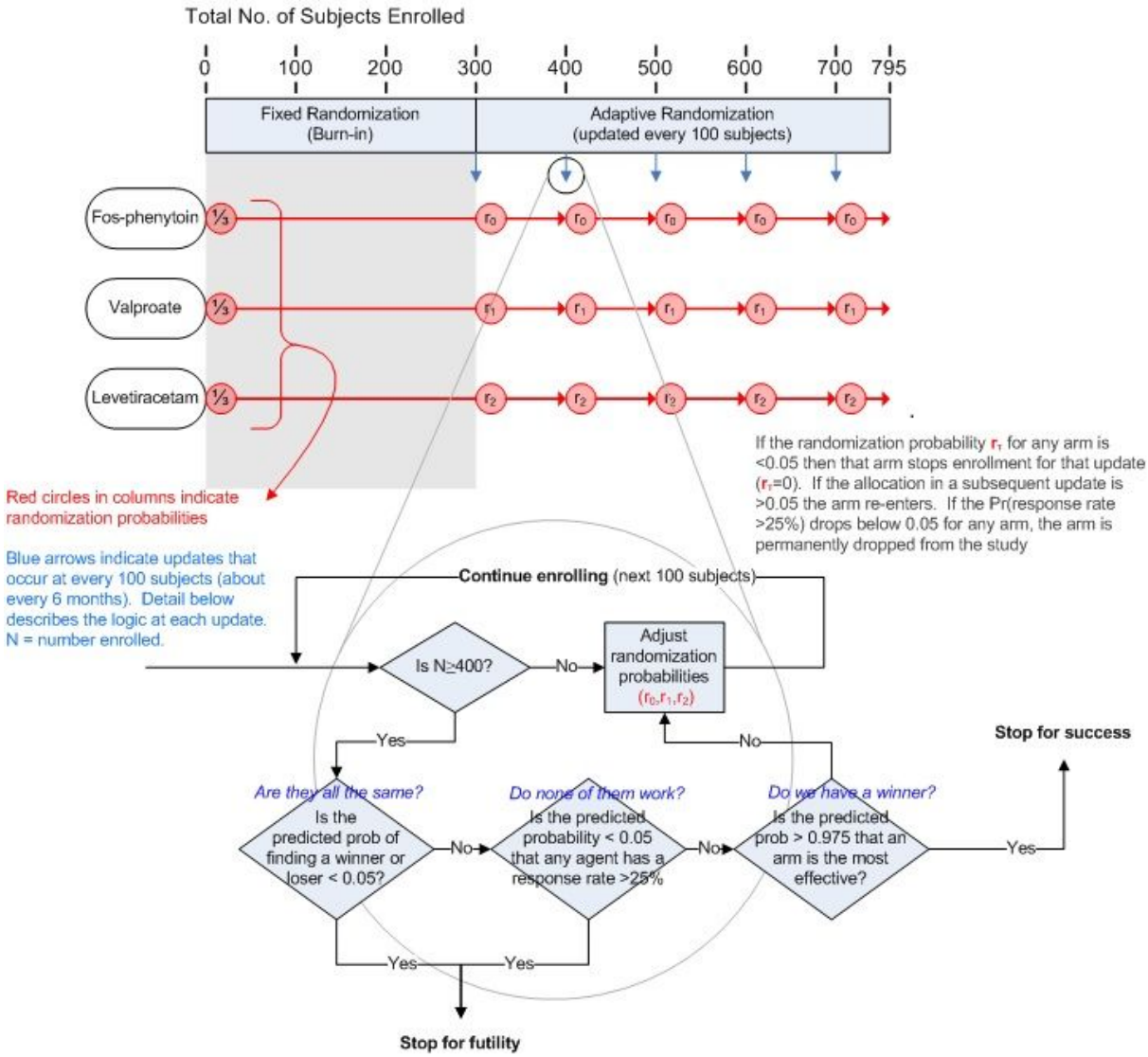

Figure 6.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

Patients will be included in this study if they are aged 2 or older, have been treated for generalized convulsive seizure of greater than 5 minutes duration with adequate doses of benzodiazepines, and who continue to have persistent or recurrent convulsions in the emergency department at least 5 minutes and no more than 30 minutes after the last dose of benzodiazepine. The inclusion criteria is intended to describe the population of patients for whom progression to second line anticonvulsants are indicated. The seizure and its initial treatment may have occurred prior to arrival in the ED.

Adequate doses of benzodiazepines for this study are determined to be: diazepam 10 mg IV, lorazepam 4 mg IV or midazolam 10 mg IV or IM for those greater than or equal to 40 kg. For children less than 40 kg adequate doses are: diazepam 0.3 mg/kg IV, lorazepam 0.1 mg/kg IV and midazolam 0.3mg/kg IM or 0.2 mg/kg IV. These drugs may have been administered in two or more divided doses. The last dose of benzodiazepine must be given at least 5 minutes prior study drug initiation to provide this dose sufficient time to act. The last dose of benzodiazepine must be given within 30 minutes of study drug initiation to avoid enrolling patients in whom re-dosing of benzodiazepines may be more appropriate. Transmucosal benzodiazepines such as rectal diazepam or buccal midazolam given at home prior to EMS arrival may be included in the calculation of the cumulative adequate benzodiazepine dose, but at least one dose of benzodiazepines must be also given by EMS or in the ED between 5 and 30 minutes of study drug administration. There is no maximum dose of benzodiazepines imposed by this trial. Although these doses are considered the minimum adequate doses based on common clinical practice, it is recommended that the best practice (subject to local standards of care) is to administer 20 mg of diazepam, 8 mg of lorazepam, or 20 mg of midazolam in adults prior to progression to enrollment.

Table 1. Inclusion criteria and rationale

Inclusion criteria	Measure	Rationale
Patient witnessed to seize for greater than 5 minute duration prior to treatment with study drug	Witness or EMS report or clinical observation	PHTSE and RAMPART study suggest that the treatment of SE should begin when single seizure or recurrent seizures without recovery of consciousness have lasted more than 5 minutes.
Patient received adequate dose of benzodiazepines. The last dose of a benzo was administered in the 5-30 minutes prior to study drug administration. The doses may be divided.	EMS or ED record of treatment: For those ≥ 40 kg adequate doses are: diazepam 10 mg IV or PR, or lorazepam 4 mg IV, or midazolam 10 mg IM or IV. For those <40 kg adequate doses are: diazepam 0.3 mg/kg IV or PR, or lorazepam 0.1 mg/kg IV, or midazolam 0.3mg/kg IM - 0.2 mg/kg IV	According to current treatment guidelines initial therapy for SE is appropriate doses of these drugs. The 5 to 30 minute window is intended to provide the last dose sufficient time to act and to avoid enrolling patients in whom the last dose may have already worn off.
Continued or recurring seizure in the Emergency Department	Clinical observation	When patient fails to respond to adequate doses of benzodiazepines, a second line agent is needed to terminate SE.
Age 2 years or older	Caretakers report of age or clinical observation	The causes and treatment of SE in patients less than 2 years of age are different from those in older children and adults.

4.2 Exclusion Criteria

ESETT is intended to be broadly inclusive of the target population. The purpose of the exclusion criteria to prevent enrollment for three narrow categories of patients: those who can or should not be enrolled under EFIC, those who have already received confounding therapy, and those with medical contraindications to the study drugs or an indication for alternative treatment. Specific contraindications are listed and explained in table 2.

Table 2. Exclusion criteria and rationale

Criteria	Measure	Rationale
Known pregnancy	History and physical exam*	Pregnant women are excluded from studies performed under exception from informed consent (EFIC).
Prisoner	Look for prison guards	Prisoners are excluded from studies performed under exception from informed consent (EFIC).
Opt-out identification	Look for medical-alert jewelry, bracelets, or trial-specific wrist bands labelled with "ESETT declined"	Provides a mechanism for those who wish to identify themselves prospectively to opt out of EFIC, or to identify and exclude cooperative potential re-enrollers.
Treatment with a second line anticonvulsant (FOS, PHT, VPA, LEV, phenobarbital or other agents defined in the MoP) for this episode of SE	Medication administration record	The use of any second line agents prior to enrollment in the study would confound determination of the effects of the study drugs.
Treatment with sedatives with anticonvulsant properties other than benzodiazepines (propofol, etomidate, ketamine or other agents defined in the MoP)	Medication administration record	Anticonvulsant sedative drugs are used for sedation and rapid sequence intubation. These drugs could terminate SE and would confound the primary efficacy outcome.
Endotracheal Intubation	History and examination	Prevents evaluation of patient for responsiveness.
Acute traumatic brain injury	Clinical history, evidence of head trauma	Other care, often requiring sedation, takes precedence.
Known metabolic disorder	Clinical history*	Patients with metabolic disorders are at risk for

		liver failure when treated with VPA (VPA package insert).
Known liver disease	Clinical history*	Patients with liver disease are at risk for liver failure when treated with VPA (VPA package insert)
Known severe renal impairment	Clinical history*	Severe renal impairment has been associated with reduced plasma protein binding of valproic acid and fosphenytoin, resulting in substantially elevated free concentrations of these drugs
Known allergy or other known contraindication to FOS, PHT, LEV, or VPA	Clinical history	As per package inserts for FOS, LEV, and VPA.
Hypoglycemia < 50 mg/dL	Finger-stick glucose	SE due to hypoglycemia is first treated by giving glucose and correcting it.
Hyperglycemia > 400 mg/dL	Finger-stick glucose	SE due to hyperglycemia is first treated by reducing glucose and correcting it.
Cardiac arrest / post-anoxic seizures	History and ECG rhythm strip	Prognosis of SE due to anoxia and cardiac arrest is uniformly poor and distinct from other causes.

* Laboratory testing is not indicated to screen for these exclusion criteria because the risk of delay in treatment is much greater than the risk enrollment with these conditions.

5. Informed Consent and Exception from Informed Consent (EFIC)

Respect for human subjects and their safety are paramount in this trial. Research involving subjects who have SE, however, presents an ethical challenge. Protecting patient autonomy through the informed consent process is typically an ethical cornerstone of human subjects research, but because patients in generalized SE are unconscious, an informed consent process is not possible and patients cannot say whether or not they would want to participate in the research. Furthermore the alternative process of identifying and obtaining surrogate informed consent from a legally authorized representative (LAR) is not practicable in SE, because the emergency treatment being studied must be initiated as quickly as possible to safely care for the patient. Identification of the optimal emergency care for those in SE in this trial can therefore only be conducted with exception from informed consent (EFIC) for emergency research. This section will explain the processes used in this trial and the detailed rationale for compliance with the FDA regulations for EFIC found at 21 CFR 50.24.

5.1 Enrollments all performed under EFIC

All participants will be enrolled under EFIC. In this trial there will be no circumstance in which an informed consent process can be meaningfully or safely performed. All patients eligible for this trial must be unconscious from generalized SE, so no one can consent for themselves, and the rapidity with which treatment is needed for SE precludes obtaining consent from parents and other legally authorized representatives (LAR) even if they are present. Emergency treatment must be given quickly because every minute of delay decreases the likelihood that an anticonvulsant medication will be effective at terminating seizures, and patient morbidity and mortality increase with increasing seizure duration. Therefore, the delay related to any meaningful and compliant informed consent process is unsafe, impracticable, and would not be ethical. It is also not practicable to identify and consent patients prior to developing SE as 35-50% of patients who have SE are new onset, and even in patients with epilepsy, SE is a relatively uncommon and unpredictable manifestation. It is not possible to predict who will have SE.

A more detailed EFIC Plan document for the trial can be found in the Manual of Procedures (MoP). The investigational new drug application for this trial is identified as using EFIC. Investigators at each site will perform community consultation and public disclosure as discussed below, and these will be reviewed and approved by local institutional review boards prior to starting the trial at the site.

5.2 Consent to Continue Participation

Subjects or their LAR will be notified of enrollment as early as possible and consent to continue participation in the study will be sought for all subjects.

Attempts are typically initiated in the ED by the study team to discuss the enrollment with the subject in those subjects who are waking up, or to locate and communicate with an LAR for subjects who are not waking up. When a subject or LAR are first available to participate in an informed consent process, they will be asked to continue participation in the study. Continuation in the study only involves further review of the subject's medical record through the shorter of hospital discharge or 30 days. Those wishing to continue will have the informed consent document explained to them, will have any questions answered, and they will be asked to review and sign the informed consent document. In those who wish to discontinue participation, no further data will be collected. Data collected prior to withdrawal will remain in the study database as per FDA requirements and guidance. Those wishing to discontinue participation will also have the informed consent document explained to them, will have any questions answered and will be asked to review and sign an informed withdrawal from the study, however, subjects are not required to complete this document in order to withdraw. Standard consent procedures will be used. A copy of a model informed consent document will be provided to sites.

If a subject is randomized into ESETT and dies before a legally authorized representative or family member can be contacted, a reliable mailing address for the subject's family or LAR will be obtained. After allowing a two to four week period of grieving, the site study team will send a letter with basic information about the clinical investigation, the subject's inclusion, and contact information so that families can call or write to obtain more information or to get questions answered if desired.

5.3 Assessment of Notification and Consent Processes

Notification and informed consent logs are incorporated in the study case report forms and will allow tracking and reporting of the timeliness of these processes. In addition, subjects and LAR's participating in notification and consent processes may be offered an opportunity to share their experience and attitudes by answering a standardized survey up to day following an informed consent or withdrawal. This information will be used for process improvement and to better understand the subject or LAR perspective on emergency research.

5.4 Compliance with Criteria and Processes Required for EFIC

FDA regulations identify the specific circumstances in which EFIC is appropriate. ESETT fulfills these requirements for emergency research. In the following section, the components of the regulation are reproduced, along with an explanation of how ESETT will comply with each requirement.

SE is life-threatening and available treatments are unsatisfactory or unproven.

21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments

are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

Population studies of the incidence of SE report an incidence of between 41-61/100,000. The mortality rate is estimated to be greater than 17% (Neligan 2010).

The Cochrane review of anticonvulsant therapy for SE found eleven studies with 2017 subjects. The review concluded that lorazepam was the most effective agent and will terminate SE in only 60-70% of patients with this life-threatening condition. Because 30-40% of patients do not respond to first-line therapy for SE, benzodiazepines are unsatisfactory on their own. The three anticonvulsant medications studied in this trial are often used as second-line therapy to treat these patients but are unproven. There are no randomized, prospective, adequately controlled trials to confirm whether one or more of these medications are either effective or safe in these patients.

Clinical trials are clearly needed. No blinded, sufficiently powered prospective, randomized controlled trial has compared treatments for seizures refractory to initial benzodiazepine treatment. Currently published treatment guidelines recommend intravenous FOS as second-line treatment, with LEV and VPA as alternatives (Brophy 2012; Loddenkemper 2011; Meierkord 2010). However, there are small, open-label randomized studies that suggest the potential efficacy of VPA over LEV in treatment of ESE (Alvarez 2011). A series of clinical observations suggest that LEV and VPA are safe and effective in the treatment of ESE (Trinka 2009; Trinka 2011).

Obtaining prospective informed consent is not feasible.

21 CFR 50.24(a)(2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

Subjects in generalized status epilepticus are unconscious and unable to provide informed consent due to their medical condition. The care of patients in status epilepticus must be initiated immediately, which, in the Emergency Department care of patients with benzodiazepine refractory SE is the immediate initiation of second line anticonvulsant therapy.

Complications of prolonged seizures include impaired ventilation and subsequent pulmonary aspiration, cardiac dysrhythmias, derangements of metabolic and autonomic function, and direct injury to the nervous system. Seizures of short duration may be clinically benign, but longer durations are associated with increasingly severe morbidity and mortality. There is no specific identifiable threshold for seizure duration that predicts the onset of morbidity, and

thus, clinical practice is geared toward terminating seizures as quickly as possible.

Clinical data have demonstrated the duration of SE is associated with death and unfavorable neurologic outcomes (Maegaki 2005, Holtkamp 2005). While many of these data concern long durations of SE lasting hours or days, data also suggest that differences of as little as a few minutes in seizure duration are also associated with differences in outcome. Patients found in SE by paramedics who had termination of their seizures prior to arrival to the emergency department have an ICU admission rate of 32% as compared to 73% in patients whose seizures persisted on arrival to the ED. In a randomized trial, patients with SE treated with lorazepam or diazepam in the field by paramedics had mortality at hospital discharge of 7.7% and 4.5% respectively, which was less than half the mortality of 15.7% for patients in whom benzodiazepines were given only after arrival in the ED (Alldredge 2001).

The benefits of emergent treatment and termination of SE likely result from minimizing the consequences of impaired ventilation, pulmonary aspiration, hemodynamic instability, or metabolic derangements associated with prolonged convulsions. Rapid termination of seizures may also prevent kindling effects demonstrated in animal models in which seizures become more refractory to subsequent treatment as the duration of seizure increases (Morimoto 2004). Rapid treatment may also prevent the neuronal cell injury and loss that occurs with increasing duration of seizures due to duration dependent cytokine mediated effects (Ravizza 2005).

Since status epilepticus is precipitated by a variety of acute and unpredictable etiologies, there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research. Furthermore, status epilepticus is often an initial presenting manifestation of disease, precluding prospective identification. This was confirmed in data from Baren et al that found prospective identification of subjects for the PECARN Pediatric Seizure Study to be infeasible (Baren 2006).

Participation holds prospect of direct benefit to subjects

> *21 CFR 50.24(a)(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Participation in ESETT holds out the prospect of direct benefit to subjects. Subjects may directly benefit from participation because status epilepticus is a life-threatening condition and some of the interventions used in this study may be more effective than others. Studies in experimental SE in animals suggest that LEV may terminate established SE but that FOS, the

treatment most commonly used, fails to do so (Mazarati 1998; McDonough 2004; Prasad 2002). Some observational clinical data also suggests that FOS or its active metabolite PHT are not the most effective second-line agents (Agarwal 2007, Alvarez 2011). The use of response adaptive randomization in this trial increases the probability that those enrolled later in the trial will be more likely to be randomized to the more effective arm if there is a more effective arm.

The trial can not be practicably carried out without exception from informed consent

> *21 CFR 50.24(a)(4) The clinical investigation could not practicably be carried out without the waiver.*

This research could not be carried out without EFIC because treatment for SE needs to begin immediately upon ED arrival. Since SE patients are unable to consent for themselves and there is not time to obtain consent from an LAR, all patients must be enrolled under EFIC. A meaningful informed consent process requires that the LAR have time to understand the material presented, be able to ask questions and have time to think about what the patient would want. This is not possible in the brief period in which the study drug is obtained and initiated. In ESE, time to treatment is especially critical. Inability to obtain informed consent can limit the ability to discover better treatments for this critical and life-threatening condition.

Need for immediate treatment of status epilepticus precludes consent from an LAR

> *21 CFR 50.24 (a)(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.*

The narrow therapeutic window described above, the inability of patients with SE to communicate, and the inherent delay in delivery of standard therapy in attempts to contact and discuss consent with a surrogate decision maker preclude the possibility of obtaining informed consent for any potential subject in ESETT. Attempts to contact LAR for notification and consent to continue participation will be tracked and can be summarized and reported to the IRB at the initial and continuing reviews.

Provision of an informed consent document

> *21 CFR 50.24(a)(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.*

A written informed consent document prepared at each site for this study must be reviewed and approved by participating IRB's approving this clinical investigation. Subjects enrolled in ESETT, or their legally authorized representatives (LAR) or family, are informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity. The study team is immediately notified of the arrival of treated subjects in the emergency department (ED). An on call study team member quickly responds to the ED to complete the subject enrollment. The subject (or LAR or family) is approached, and an informed consent process initiated as soon as possible. The study team notifies the subject or LAR/family about the subject's enrollment, provides information about the study and about the subject's rights and the responsibilities of the investigators, and answers any questions about the study and further participation. A written informed consent document is used to reinforce the information provided verbally and to document a decision to either continue in the study or to not participate any further. A copy of this form is provided to the subject and another copy is placed in the research record.

Community Consultation

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn*

The community will be consulted prior to the initiation of research. With guidance from the each site's IRB, the community will be asked to give their opinions of the research. A menu of options is included in the detailed EFIC plan in the MoP and includes mechanisms such as community meetings, town hall meetings, focus groups, meetings with established community advisory boards, in-person surveys, and random-digit dialing surveys. The specific type of community consultation will be determined by each site's IRB. Reporting of community consultation results will be standardized across the ESETT sites.

Public Disclosure

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results*

Public disclosure is the primary element in making certain that ESETT is conducted in an entirely transparent manner. Methods of announcing information about the trial, and the development of advertising and other materials about the trial, will take place both locally and nationally. Public disclosure will be initiated prior to approval of the trial, may continue during enrollment, and will conclude with dissemination of study results after the trial is completed. A menu and

discussion of many public disclosure methods and procedures is detailed in the EFIC plan in the MoP. Each site IRB will determine the type and form of local public disclosure. Reporting of public disclosure efforts will be standardized. Summaries of public disclosure will be reported to each IRB, and composite reports of local and national public disclosure at the trial-level will be provided to the FDA docket.

Data Monitoring Committee

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;*

A Data and Safety Monitoring Board (DSMB) is appointed by the NINDS to provide ongoing evaluation of safety data as well as the overall conduct of the trial, per institute guidelines. The members will have a meeting with the study team prior to study commencement to discuss the protocol as well as content and format of the DSMB reports. The SDMC will prepare requested reports at specified time intervals. Data and safety monitoring will be performed consistent with the guidance provided by the NIH notices 98-084 “Policy for data and safety monitoring” and OD-00-038 “Further guidance on data and safety monitoring for phase I and phase II trials”, and by the NINDS document based on these notices “NINDS Guidelines for Data and Safety Monitoring in Clinical Trials”.

Contacting Other Family

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: …. (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

It will not be ethically possible in ESETT, for the reasons described above, to delay treatment of the seizing subject long enough to contact either an LAR or other family members. A provision of the protocol has been made to allow subjects that learn of the trial through public disclosure efforts or other means, and who would not want to participate if treated in the ED for status epilepticus, to communicate that decision to the ED without causing any delay in treatment. As part of the primary assessment of a seizing patient, ED providers already check for medical alert jewelry to ascertain emergent medical information about the patient. If the words “ESETT declined,” or alternative designation as defined in the MoP, are listed on the medical alert tag, the patient will not be enrolled in the clinical investigation. Medical alert tags are commonly used by people with epilepsy already, and provide a means of communication that does not require such patients to wear any extra marker. Since they are already worn daily, they do not require additional effort to use once information is added to the tag. The tags are common and

effective for communicating information to medics while still being inconspicuous. Use of this enrollment exclusion will be tracked and this information made available to IRBs at the time of continuing review.

Post Enrollment Notification and Consent to Continue

> *21 CFR 50.24(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.*

Subjects enrolled in ESETT, or their legally authorized representatives (LAR) or family, are informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity as detailed above and in the MoP. It is anticipated that the notification of subjects, or their families or LAR, will most commonly take place in the ED within hours of subject enrollment. Attempts to notify the subject or an LAR are repeated until successful. All notification attempts are logged and recorded in the subjects online case report form in WebDCU™. Reports of these logs will be available for inclusion in annual reports to the respective IRBs.

Record Keeping

> *21 CFR 50.24(c) Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA.*

Records documenting the enrollment of patients using EFIC, procedures for notification of enrollment, and informed consent forms will be kept for a minimum of three years after completion of the clinical investigation.

IND Requirement

> *21 CFR 50.24(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as*

amendments under Secs. 312.30 or 812.35 of this chapter.

This trial requires an IND, review and approval by the FDA. No enrollment can commence unless approval by the FDA and participating IRBs is obtained. The Study Principal Investigator serves as the sponsor of the IND. Discussions with the FDA have clarified that a single IND is appropriate for the proposed trial.

Communication of IRB Determinations

> *21 CFR 50.24(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.*

If an application for ESETT is disapproved by a local IRB at any site, the Hub principal investigator will inform the ESETT principal investigator and IND sponsor and provide him with the written findings of that IRB. The Study PI/sponsor will promptly disclose this information to the FDA, and to all participating Hub PIs who will be instructed to submit these to all IRBs to which applications for ESETT have been submitted for review. If there is a change in the study protocol, then there must be a re-review of the protocol by all the IRBs of the participating institutions.

6. STUDY ENROLLMENT PROCEDURE

6.1 Screening

The goal is to include all eligible patients who present to participating EDs. All patients presenting with a diagnosis of seizures or convulsions will be evaluated for participation in the study. A screen failure log will include patients with a diagnosis of seizures or status epilepticus who are not randomized into ESETT.

6.2 Enrollment

Study processes will not delay clinical treatment. When an eligible patient presents to the emergency department, the clinical team will access the age appropriate ESETT "use next" box. To ensure treatment is not delayed, the "use next" box must be easily accessible and maintained in proximity to patient care in the ED. Most often, this will be in the secured ED medication dispensing system or the ED pharmacy.

The clinical team opens the "use next" box. The protocol assist device is activated. The weight based infusion rate is determined from the dose administration chart. If the patient is a child, the length based weight estimation tool is used to determine dose unless an accurate weight is known. An infusion pump is programmed with the determined rate and the infusion line is primed. The infusion is then started and the timer is started on the protocol assist device.

The study team should be alerted at this time, if not already done.

Study drug is administered by pump for ten minutes (except as noted in section 7.3). The infusion is then discontinued and discarded. The patient should then be observed for 10 more minutes, until 20 minutes after the start of study drug infusion. Rescue therapy is not indicated during this period. After 10 minutes from the end of study drug infusion, rescue therapy should be given as deemed clinically indicated by the care team for persistent or recurrent seizures.

The primary outcome is determined at 60 minutes.

6.3 Study Team Arrival

The study team should be activated as early as possible without delaying treatment. The care team follows the protocol but does not engage in research. Questions about eligibility are determined by the study team. The study team will arrive in the ED as soon as possible.

Upon arrival, the study team will assist the clinical team in completing the protocol. After arrival the study team will seek an LAR to notify of the subject's participation and to determine consent to continue. The study team maintains a log of attempts to locate an LAR, of notifications, and of consent decisions.

The study team will collect and complete the ED-enrollment case report form, will collect the spent “use next” box and protocol assist device, and will process, reload, and place a new “use next” box.

6.4 Blood Draw

Up to 2 tubes of blood, approximately 5 mL total (2.5 mL each), may be drawn from a subset of subjects after the study drug infusion to confirm drug levels and accurate assignment as needed to ensure study performance.

6.5 Enrollment Flow Diagram

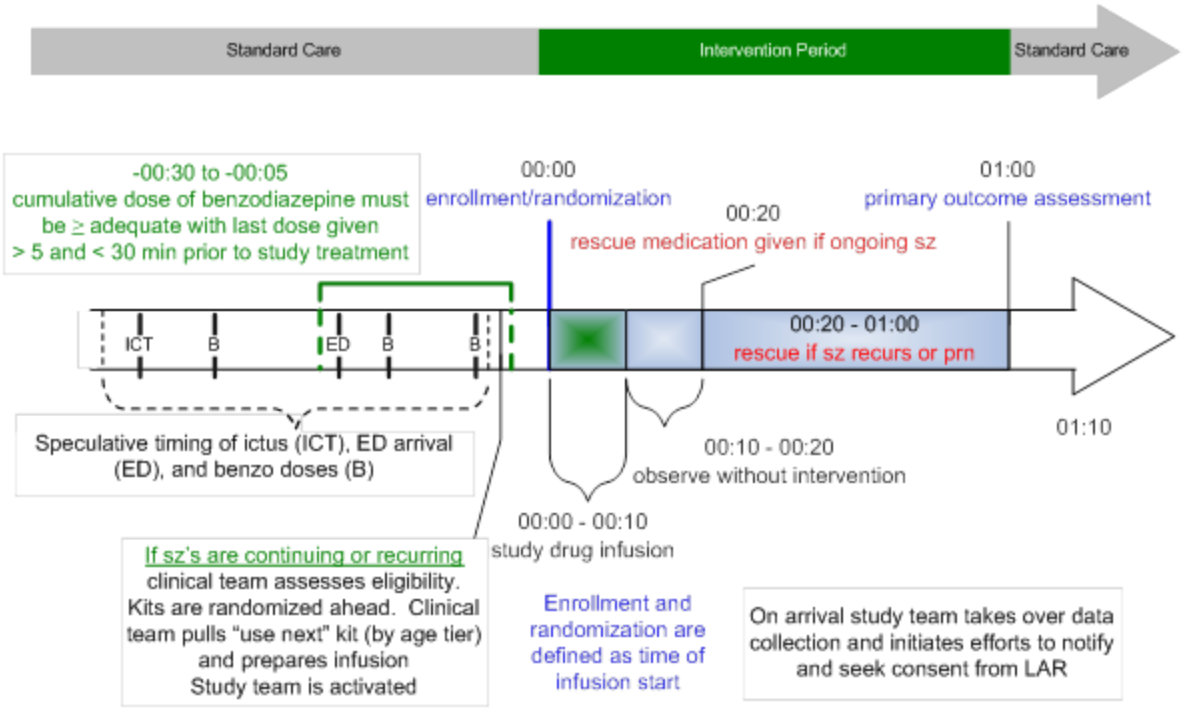

Figure 7.

7. STUDY INTERVENTIONS

7.1 Determination of subject weight

The rate of study drug infusion is based on estimated patient weight. The subject's weight may be obtained from reliable caregivers or records. In children, if an accurate weight is not known, dose will be determined using the length-based weight/dose estimation tool included in the "use next" box, (akin to the Broselow tape). In adults and the elderly, weight will be estimated in the manner as in standard care for weight-based dosing of other resuscitation/critical care drugs. A measured weight may also be used if available, but it is expected that the clinical scenario will usually preclude weighing the subject.

7.2 Study drug administration

Study drugs will be administered intravenously. For purposes of this study, intraosseous (IO) access will always be considered equivalent to IV access. Infusion pumps will be used to ensure that study drug is administered over 10 minutes.

The infusion pump will be programmed to deliver the volume/rate indicated on the dose administration chart (table 3). The volume and rate will be confirmed by a second nurse. Infusion will last 10 minutes. Priming the line prior to infusion and flushing the line at the end of infusion are performed in a manner that ensures the entire study volume of study drug is delivered in accordance with local nursing practice.

Table 3. Dose Administration Chart

Subject Wt (kg)	Infusion Vol. (mL)	Infusion Rate (mL/min) over 10 min	FOS dose (mg)	LEV dose (mg)	VPA dose (mg)
7.5	9	0.9	150	450	300
10	12	1.2	200	600	400
12.5	15	1.5	250	750	500
15	18	1.8	300	900	600
20	24	2.4	400	1200	800
25	30	3	500	1500	1000
30	36	3.6	600	1800	1200
35	42	4.2	700	2100	1400
40	48	4.8	800	2400	1600
50	60	6	1000	3000	2000
60	72	7.2	1200	3600	2400
70	84	8.4	1400	4200	2800
75	90	9	1500	4500	3000
>75	90	9	1500	4500	3000

7.3 Study Drug Infusion Precautions

Study drug infusion precautions are the same as in standard care in patients with status epilepticus. Heart rate and rhythm, blood pressure, and oxygen saturation are monitored.

If hypotension or cardiac arrhythmia occur during study drug infusion, the infusion rate will be reduced by 50% (increasing the infusion time and maintaining the planned volume).

In this context, hypotension is defined as sustained systolic blood pressure <90 mm Hg in subjects 13 years and older, <80 mm Hg for 7 years to <13 years, and <70 mm Hg for 2 years to <7 years. Intravenous fluid may also be used for initial treatment of hypotension.

If hypotension or cardiac arrhythmia persist, or as determined appropriate by the care team, the drug infusion will be discontinued. Persistent hypotension or arrhythmia will be treated according to local standard care after the study drug is stopped.

Treatment with study drug may also be terminated for any serious adverse event during infusion that the treating physician believes is study drug related.

Discontinuation of study drug does not affect participation of the subject in the study. All subjects should be followed until they reach their end of study.

7.4 Randomization

Due to the emergency nature of ESE, randomization must not delay treatment. To complete the randomization quickly, the study drug will be preassigned using a central randomization process via WebDCU. The mortality associated with SE and etiology of SE varies with age. In addition, certain adverse effects of drugs such as hypotension are more common in the elderly compared to the pediatric age group. For these reasons, randomization assignments will be stratified by age group (2-18 years, 19-65 years, and greater than 65 years).

Prior to enrollment at each site, the randomization assignment is made [for each of the three age strata]. The assigned study drug is installed in the "use next" box. When the next eligible subject at the clinical site is identified, the ED nurse or physician, selects the "use next" box [for that stratum].

Once the infusion pump, connected to study drug vial and patient's IV catheter, is turned on, the patient is considered to have been randomized into the study. After a patient is randomized and the study team member enters the randomization form into WebDCU, the next treatment assignment is made, and a new "use next" box can be prepared. Hence, after each subject is randomized, the treatment assignment is made for the subsequent subject (within that stratum) once the current subject's randomization data are entered into WebDCU.

Sites may also be contacted and asked to go to WebDCU to reassign the content of the "use next" box when randomization in the trial is updated.

7.5 Study Drug

Study drug will be produced at the central pharmacy, a GMP facility at University of California, Davis. Diluted formulations are expected to remain stable for months when stored at 4-8 ^{O}C. Expiration dates for study drug will be determined and adjusted based upon ongoing stability testing performed on study drugs prepared at the GMP facility for the study.

All three formulations will be pale yellow solutions. None are reported to consistently cause infusion-site adverse effects. The method of drug administration, including volume and rate of

infusion is identical for all three drugs. These factors ensure that drug administration will be blinded.

The drugs will be formulated in the following concentrations: FOS 16.66 mg/ml, VPA 33.33 mg/ml and LEV 50 mg/ml. The dose will be FOS 20 mg/kg, VPA 40 mg/kg, and LEV 60 mg/kg, increasing up to a weight of 75 kg. At this weight the maximum safe dose for a 10 minute infusion period for adults is reached. A 10 kg patient would receive drug infusion at the rate of 1.2 ml/min and those weighing 75 kg or more will receive drugs at an infusion rate of 9 ml/min.

7.6 Study Drug Packaging

Study drug will be prepared in 100 mL glass vials, labeled as investigational, and coded with unique human readable ID numbers and barcodes. Because this is a blinded study, nobody at the site (local pharmacy, clinical team, and study team) will know whether the next assignment is FOS, VPA, or LEV.

"Use next" boxes will be prepared at the site and contain: 1) a 100 ml glass vial containing either FOS, VPA, or LEV, 2) a dose administration chart, 3) a protocol assist device, and 4) a length based weight/dose estimation tape (similar to Broselow tape).

7.7 Protocol Assist Device

The protocol assist device is a mobile electronic platform, such as the Apple iPod Touch, with an ESETT app loaded on it. It is intended to assist the clinical and study team in performing the study protocol. The app will be started by the treating physician or nurse and will guide the team through the initial phase of the study. The device is intended to serve several functions including: confirmation of correct randomization code, time keeping during infusion and evaluation, supplemental data logging, and support of rapid emergency unblinding.

The protocol assist device should be kept at subject's bedside until retrieved by the study team.

8. OUTCOME ASSESSMENT AND POST-INTERVENTION

8.1 Assessment of treatment effect

Assessment of treatment effect is performed at 20 minutes and 60 minutes after the start of study drug infusion.

"Start of study drug infusion" is considered the time of randomization. It is the time when the study drug infusion is begun by starting the IV infusion pump.

Absence of clinically apparent seizure at 20 and 60 minutes is determined clinically. Clinically apparent seizure is defined as obvious focal or generalized tonic clonic movements, nystagmoid or rhythmic eye movements, or generalized or segmental myoclonus at the time of assessment.

Patient's responsiveness to verbal command or noxious stimuli is observed at 20 and 60 minutes. Responsiveness at time of assessment is always compared to that at the time of randomization. Generally, improvements in responsiveness are characterized by purposeful responses to noxious stimuli, the ability to follow commands, or verbalization. The Richmond Agitation Scale Score will be recorded and may be used to assist in this determination.

8.2 Determination of primary outcome

The primary outcome will be determined 60 minutes after the start of study drug infusion. The primary outcome may be determined by the study team if present, or by a treating ED physician on the clinical team if the study team is not yet available. The primary outcome is based upon the assessment of treatment effect at 60 minutes as defined above, and the use of additional anti-seizure medications. Ongoing seizures at the time of determination of the primary outcome, whether persistently or recurringly, indicates a failure to meet the primary outcome. Transient seizure recurrence followed by cessation, however, is consistent with meeting the primary outcome.

Medications qualifying as "anti-seizure medications" for the purpose of determining the primary outcome are detailed in the study Manual of Procedures. The administration of the these anticonvulsant or sedative medications for recurrent seizures or any other reason, by any route, within 60 minutes after the start of study drug infusion indicates a failure to meet the primary outcome.

The primary outcome should be based on the assessment of what the treatment effect and the condition of the patient were at 60 minutes after the start of study drug infusion based upon all information available to the assessor at the time the primary outcome is documented.

Death prior to 60 minutes after the start of study drug infusion indicates a failure to meet the primary outcome.

The primary outcome may be documented in more than one location. The highest level of source document in the established hierarchy will be considered the primary source document for the primary outcome. The hierarchy of source documents that will be used to confirm the primary outcome outcome is:

1. Contemporaneous direct data entry. If the primary outcome is directly entered into the CRF in WebDCU at the bedside, the CRF itself will be considered the primary source document.
2. Study book form worksheet. If a paper version of the CRF is used as a worksheet, that worksheet will be used to complete the CRF in WebDCU and must be maintained in the study binder and considered the primary source document.
3. Protocol Assist Device. The primary outcome recorded on the protocol assist device will be treated as a source document and may be used as an electronic CRF worksheet from which to complete the CRF.
4. Medical Record - study note template. The clinical medical record may also be the source document. A templated study note takes precedence among medical records.
5. Medical Record - adjudicated. If there is no structured source of the primary outcome, the medical record will be the source and the adjudicated primary outcome used.

8.3 Determination of secondary outcomes

The primary safety outcome is the absence of life threatening hypotension and cardiac arrhythmia within 60 minutes of the start of study drug infusion.

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.

Life-threatening cardiac arrhythmia is defined as any arrhythmia that persists despite reducing rate of study drug infusion, and that requires termination with chest compressions, pacing, defibrillation, or use of an antiarrhythmic agent or procedure.

Additional predefined safety outcomes include mortality, need for endotracheal intubation within 60 minutes of start of study drug infusion, Richmond agitation and sedation score (RASS) at 60 minutes, acute seizure recurrence within 12 hours, and acute anaphylaxis.

Mortality is determined by survival to subject end-of-study (hospital discharge or 30 days, whichever comes first). All causes of mortality are included.

Need for endotracheal intubation within 60 minutes of start of study drug infusion includes any placement or attempt at placement of a definitive tracheal airway (orotracheal, nasotracheal, cricothyroidotomy, or tracheostomy) for support of respirations or protection of airway. The use of non-definitive and/or non-tracheal airways (oral or nasal airways, laryngeal mask airways, or esophageal obturator airways) is not included if the patient is not subsequently intubated unless specifically deemed to have been used in lieu of tracheal intubation.

The RASS may be determined by the care team or the study team. The RASS scoring system is fully described in the manual of procedures.

Acute recurrent seizure is defined as definitive convulsive or electroencephalographic seizure activity triggering further anticonvulsant therapy occurring between 60 minutes and 12 hours after the start of study drug infusion. This definition does not include those given further anticonvulsants as secondary prophylaxis or as treatment for vague or uncertain exam findings or nondiagnostic electroencephalography.

Acute anaphylaxis is defined as a clinical presentation consistent with life threatening allergic reaction occurring within 6 hours of the start of study drug infusions and manifested as urticaria in combination with either (1) a systolic blood pressure of < 90 mmHg sustained for greater than 5 minutes, or (2) objective evidence of airway obstruction, and for which the patient was treated with antihistamines and/or steroids.

Respiratory depression is defined as impairment of ventilation or oxygenation necessitating definitive endotracheal intubation and mechanical ventilation. It is distinct from intubations performed only for airway protection in those with decreased levels of consciousness. It does not include those getting only supraglottic airways or transient bag-valve-mask support.

Secondary efficacy outcomes include time to termination of seizures, admission to ICU, and the length of ICU and hospital stays.

The time to termination of seizures is the interval from the start of infusion of study drug to cessation of clinically apparent seizure in those who meet the primary outcome.

Hospital and ICU admission from the ED, and length of stay, is abstracted from the hospital admission record. ICU admission is recorded as occurring only if the ICU is the initial inpatient unit for the patient. Length of stay is determined by the number of calendar days after the day of ED arrival until hospital discharge or subject end-of-study.

8.4 Endotracheal intubation

Elective or semi-elective endotracheal intubation (e.g. for imaging studies, etc.) should be delayed until after determination of primary outcome if possible. Emergency endotracheal intubation should not be delayed. The need for emergency intubation is determined by the

care team. It is generally not necessary to perform emergency endotracheal intubation for prolonged unresponsiveness alone in this patient population. Emergent or elective endotracheal intubation and its indication should be carefully documented, including all medications administered.

8.5 Rescue anticonvulsants

Subjects who do not respond to the study drug and continue to seize >20 minutes after the start of study drug infusion (>10 minutes after the completion of study drug infusion) will need additional anticonvulsant therapy for SE at the discretion of the treating team. The treating physician will follow local practice guidelines in choice of a third line agent for the treatment of SE. Appropriate third line choices include phenobarbital or a general anesthetic such as propofol, midazolam or pentobarbital when a second-line agent has failed. Finally, some centers may choose to use another second line agent. If the care team feels that another second line agent is indicated and that knowledge of the study drug given is needed to guide this selection, emergency unblinding should proceed as described below in section 10.2.

8.6 Continuous EEG

Continuous EEG should be performed as indicated by the care team consistent with standard clinical practice. If indicated, cEEG should be initiated as early as possible.

8.7 Standard supportive care

Other than as indicated in this protocol, subjects will receive the usual care and evaluation provided at each site. Sites may wish to reference the practice parameter recommendations for status epilepticus of the American Academy of Neurology (Riviello 2006).

9. ADVERSE EVENTS

9.1 Definitions of Adverse Events:

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

A Serious Adverse Event (SAE) is any adverse event that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, or requires intervention to prevent permanent impairment or damage. For the purposes of this study, we specifically exclude hospitalization for the sole purpose of observing a patient after SE as a Serious Adverse Event.

9.2 Grading of Adverse Events

All adverse events (AEs) occurring within 24 hours of treatment and all serious adverse events occurring during study participation will be documented on the AE case report form. The severity of adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (Version 4.03, June 2010, CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v 4.03) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Table 4.

Grades	Descriptions of severity for each AE based on this general guideline
Grade 1 Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 Moderate	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3 Severe	medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4 Life-threatening	urgent intervention indicated
Grade 5 Fatal	Death related to AE

Severity is not equivalent to seriousness. A serious adverse event (SAE) would be any event in

category 4 or 5, and any event in category 3 that required or prolonged hospitalization. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade Selection i.e., Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

9.3 Relationship to Study Treatment

One of the most important components of AE reporting is determining the cause of the AE. It is imperative that the investigator assess AE causality in terms of overall study participation and make an independent determination as to whether the AE was thought to be related to any study-related activity (i.e., study intervention,). Determination may be particularly challenging in ESETT since typical criteria for assessing causality such as evaluation of the effects of de-challenge and re-challenge are not possible within the scope of this protocol in which study interventions are isolated single exposures of short acting medications. In addition the underlying cause of SE: stroke, infection, inflammation etc. cause adverse events. Finally, prolonged seizures of SE cause adverse events. For each adverse event, the relationship to the study treatment must be recorded as definitely, probably, possibly, unlikely, not related. The NETT modified "Algorithm to Determine Relationship of Adverse Event to Study Agent" will be used for all relatedness determinations in ESETT, and is found in the Manual of Procedures.

9.4 Adverse Event Reporting

All AEs occurring within 24 hours of study treatment and all serious adverse events (SAEs) occurring until participation in study has ended (discharge from the hospital, death, or 30 days since enrollment) are recorded on the online AE case report form (CRF) through the WebDCU™. The site PI or Study Coordinator or designee is responsible for entering all AEs and SAEs and updating the information (e.g., date of resolution, action taken) in a timely manner. All non-serious AEs must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. For SAEs, the data entry must take place within 24 hours of discovery of the event.

The site PI is responsible for the monitoring and follow-up of AEs until resolution (or end of study for that subject) and appropriate documentation in the subject research record. In addition to performing protocol-specified follow up, the participating PI must review all previously reported ongoing AEs to evaluate the current status. If an AE that was previously reported on the Adverse Event CRF fully resolves and then recurs at a later date, the second occurrence is considered a new AE and a new Adverse Event CRF must be completed. Likewise, if an SAE that was previously reported and subsequently fully resolved later recurs at a level requiring expedited reporting, the SAE must be reported as a new SAE on the Adverse Event CRF.

9.5 Expected Adverse Events

Expected adverse events include side effects known to be potentially associated with the study medications as listed in the study drug package inserts, and complications that commonly occur as a result of the underlying condition or as a result of hospital care. The outcomes and events defined below are likely and anticipated and will be closely tracked.

These include the secondary safety outcomes previously defined in section 8.3:

- Life-threatening hypotension
- Life-threatening cardiac arrhythmia
- Mortality
- Need for endotracheal intubation
- RASS
- Acute recurrent seizure
- Acute anaphylaxis
- Respiratory depression or failure resulting in intubation.

Other defined expected adverse events include:

Hepatic transaminase or ammonia elevations, defined as those levels determined by the site investigator to be greater than 3 times the upper limit of normal or otherwise clinically significant.

Purple glove syndrome, defined as the presence of all three of the findings of objective edema, discoloration, and pain in the distal extremity in which study drug was administered, with or without known extravasation, and for which there is no other evident etiology.

9.6 Clinical Management of Adverse Events

All adverse events will be managed according to local institution guidelines and treating physician's judgment. Specific recommendations for managing acute adverse events during drug infusion are included above in Section 7.3.

10. STATISTICAL CONSIDERATIONS

10.1 Randomization

The randomization scheme will be equal allocation (1:1:1) for the first 300 patients. Once 300 subjects are enrolled, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm (Connor 2013). The target allocation ratio will be updated every 100 patients. We will use a "Step Forward" centralized randomization procedure developed for emergency treatment trials. (Zhao 2010) Randomization will be stratified by age.

10.2 Blinding and unblinding:

Patients and emergency department study team members are blinded to the treatment assignment, as are the PIs and clinical coordinating center (CCC). Blinding is provided by the use of the same color of formulations, same drug packaging, and same method of drug administration in every subject.

Emergency unblinding may be required if the treating team feels that subjects' care after the study intervention requires knowledge of what study drug was given. Emergency unblinding will not be performed within 60 minutes of the start of study drug infusion. The blind should be maintained until after the primary outcome has been collected.

10.3 Primary outcome:

A patient is considered a treatment success if they meet the definition of the primary outcome as defined above.

10.4 Secondary outcomes.

Secondary outcomes are intended to show safety, congruence or divergence from the primary outcome, or to provide additional detail that helps to more fully describe or interpret the effects of the treatment, the study population, or the clinical scenario.

10.5 Primary Analysis

The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods. This trial will be considered a success if the probability that a treatment is the most effective is greater than 0.975 or the probability that a treatment is the least effective is greater than 0.975 for any treatment.

Each of the three treatment arms is modeled independently. We assume the probability of response has a uniform Beta(1,1) prior distribution. We assume the number of responses on each treatment arm follows a binomial distribution. We update the prior distribution with the observed data and use the resulting posterior distribution to calculate the probability that each

treatment is the most effective and the probability that each treatment is the least effective. The posterior distribution for each treatment arm will therefore be Beta(1+ # of Successes, 1+ # of Failures).

At the conclusion of the trial, we will report the response rates for each treatment group with 95% credible intervals and the pairwise differences in responses rates and corresponding 95% credible intervals of those differences.

10.6 Frequentist Analysis of the Primary Outcome

At the final analysis, the global null hypothesis that the probabilities of success for all three treatment groups are equal will be tested in a chi-squared test with 2 degrees of freedom. If, and only if, the three-way, global null hypothesis is rejected, then all pairwise comparisons will be performed as a two-sample test of difference in proportions (Z - test). Although the Frequentist tests will only occur once, we will use Pocock boundaries to control the overall alpha.

10.7 Interim Analyses

Interim monitoring for success and futility will begin after 400 subjects have been randomized and will be repeated after every additional 100 subjects are randomized. This trial will stop early for success if we have identified the maximum effective treatment with a least 97.5% probability.

There are two early futility criteria. The first futility rule will stop the trial early if all treatment arms have a clinically unacceptable response rate. The second futility rule will stop the trial early if all treatments are performing similarly and we will be unable to identify a most effective or least effective treatment.

Following review of both the interim analysis results and safety data, the DSMB will make a recommendation regarding the above stopping rules.

10.8 Estimated accrual

Estimates of accrual for purposes of statistical planning assume 40 enrollment sites averaging 5 subjects per year over a 4 year enrollment period.

10.9 Sample size considerations

This study will enroll a maximum total sample size of approximately 795 patients over 4 years, at an accrual rate of approximately 16.5 patients per month. A sample size of 795 provides approximately 90% power to identify the most effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (an absolute difference of 15%). The trial operating characteristics were determined via an

extensive simulation study. The statistical and full simulation details as well as the operating characteristics of the design have been published (Connor 2013).

The expected response rates for FOS, LEV and VPA are based on the retrospective analysis of 279 episodes of established SE in adults, who were treated with PHT, LEV or VPA (Alvarez 2011). The study reported 59.6% of patient episodes responded to PHT, 51.7% to LEV and 74.6% to VPA. Based on this study and expert evaluation of all currently published data on the treatment of established SE, we expect that the worst drug will be effective in 50% of the patients. A 15% difference is the minimum clinically important difference sufficient to change clinical practice.

The total sample size for this trial corresponds to the sample size that would be needed for a frequentist analysis. A sample size of 209/group (627 total) is needed for a chi-squared test with 2 degrees of freedom of the overall test of equality of the three proportions with 90% power (assuming the smallest proportion is 0.50 and the largest proportion is 0.65 and the average proportion is 0.55, two-sided alpha 0.05). For a two-sample test of proportions (all pairwise comparisons of treatment groups), with equal allocation into each treatment group, when one treatment proportion is 0.50 and the other treatment proportion is 0.65, the sample size needed is 240 per group to detect an absolute treatment difference as small as 0.15 with 90% power (assuming two-sided alpha 0.05 and interim looks). Thus, a total sample size of 240*3 groups=720 (uninflated for re-enrollers, missing data). Given the possibility of re-enrollers, protocol violations, and missing data, the maximum sample size was inflated from 720 up to 795 by N`=720*R where R=(1/(1-.025)^2)*1.05. The sample size was inflated in two ways. First, for the re-enrollers (expected to be 5%) who will be excluded from the analysis. Secondly, to account for the impact of treatment cross-overs, protocol violations, and missing data on the ITT analysis (expected to occur 2.5% of the time). In order to determine the operating characteristics for this Bayesian adaptive design, simulations were performed assuming a maximum sample size of 720 (the uninflated maximum) and considering different response rate scenarios.

10.10 Missing Data and Non-compliance

The primary analysis will be analyzed under the intent-to-treat principle (ITT). The ITT evaluable sample will include all subjects who are randomized. Subjects that are enrolled more than once during the study period will have only their first enrollment included in the primary analysis. It is anticipated that a maximum of 5% of subjects will be re-enrolled. In an ITT analysis, missing data and treatment cross-overs can be problematic. Due to the short term endpoint, minimal missing data is expected for the primary outcome. However the inability to administer the full dose of the study drug, or other protocol violations may occur and attenuate the treatment effect. It is anticipated that a maximum of 2.5% of data will be missing or involve

treatment cross-overs. Any missing values will be considered a treatment failure.

10.11 Secondary Analyses

Secondary analyses of primary outcome will include an analysis of the adjudicated primary outcome, a re-enroller analysis, a per protocol analysis, an analysis by age. Exploratory analyses of the primary outcome will assess treatment differences adjusting for etiology, time from seizure onset to randomization, and enrolling site. Clinically important differences in the treatment effect due to sex/gender, racial, or ethnic differences are not expected, but will be explored. Secondary and exploratory analyses will not be adjusted for multiple comparisons.

10.12 Analysis of Secondary Outcomes

The secondary outcomes will be compared by treatment group. All secondary outcomes will be tested at a significance level of two-sided alpha of 0.05. Binary outcomes will be compared by first testing the null hypothesis that the proportion of responses for all three treatment groups are equal in a chi-squared test. If the three-way null hypothesis is rejected, then all pairwise comparisons will be performed as two-sample tests of proportions. Continuous outcomes will be compared in an F-test to test the null hypothesis that all three treatment groups are equal, followed by pairwise t-tests. Kaplan Meier curves and log rank tests will be used to compare time to event outcomes by treatment group.

10.13 Pediatric Subgroup Analysis

The interaction of age group and treatment group will be tested at each interim analysis. If there is sufficient evidence of an interaction, then the response-adaptive randomization will be stopped and randomization will revert to equal allocation until the end of the trial.

Regardless of whether an interaction between age group and treatment is detected, the primary analysis will be redone by age group (children age 2-18, adult 19-65, and Seniors, >65).

11. DATA COLLECTION

11.1 Study activity and data collection

Follow up data collection: Very limited clinical data will be collected during hospitalization, beyond that available and collected in the ED. Hospitalized subjects should be reevaluated the day after admission for adverse events. At the end of hospitalization, subjects should again be evaluated for serious adverse events. Seizure etiology and hospital/ICU length of stay are also determined at discharge.

11.2 Data Collection Schedule

Data elements will be detailed in the CRF study book which is available for download under Project Documents on WebDCU™

Table 8. Schedule of Assessments

	Day 1 (data collected in the ED on the day of enrollment)	Day 2 (24-48 hours after study drug infusion)	End of Study*
Eligibility	X		
Randomization	X		
Primary outcome	X		
Safety outcome: hypotension; cardiac arrhythmia	X		
Richmond Agitation and Sedation score (RASS)	X		
Demographics	X		
Post enrollment consent to continue	X**		
Probable cause of status epilepticus			X
Adverse Events	X	X#	X
Endotracheal Intubation	X	X#	
EEG			X
Time to termination of seizures	X		
Admission to ICU			X
ICU length of stay			X
Hospital length of stay			X
Study Drug infusion log	X		
Prior/Concomitant meds	X		
Vital Signs	X		
End of Study			X

* Hospital Discharge or 30 days from enrollment whichever comes first

** Or earliest opportunity if not possible in the ED

Optional repeated forms

11.3 Quality assurance

The study will be conducted in accordance with the ICH Guidelines for Good Clinical Practice and all relevant local, national and international regulations.

Please refer to the NETT monitoring standard operating procedures (SOP) at http://nett.umich.edu . In brief summary, Hub investigators will provide quality assurance within their Hub spoke complex in a process that, in this network, will be called Verification. This is independent of Monitoring, which, in this network, is used to mean only independent external monitoring by the NETT Project Monitor of the Clinical Coordinating Center (CCC).

Data quality monitoring is performed continuously. Out of range and logical errors are identified at the time of data entry.

Site visits will be conducted periodically by the Project Monitor(s). Details of the content of site visits are found in the monitoring plan in the MoP. In brief, the primary purpose of the site visit is to confirm that local regulatory documents are being properly maintained, and to compare data reported on case report forms with source documents, including documentation of informed consent and proper reporting of adverse events.

Some combination of risk based allocation of site and remote source document verification will be used over the course of the trial.

11.4 Data management

The NETT Statistical and Data Management Center (SDMC) will provide data management for the ESETT study. The SDMC is housed in the Data Coordination Unit (DCU) at the Medical University of South Carolina (MUSC). Data entry will occur at the enrolling sites using a web-based data entry system, WebDCU™. A central reader form will be entered into WebDCU at the NETT CCC at the University of Michigan.

11.5 Clinical adjudication Core

The clinical adjudication core will determine key clinical characteristics for each patient enrolled including the etiology of status epilepticus and the duration of seizures prior to enrollment.

The primary outcome is based on site determination, but the adjudication core will review all primary outcomes for consistency and will determine the reasons for failure of therapy in those patients who do not meet the primary outcome. Packets of de-identified medical records will be available to the adjudicators as needed. The adjudicators will be blinded to treatment assignment.

12. HUMAN SUBJECTS

The protection of human subjects is of primary importance in clinical research and in this clinical trial. Clinical treatment teams must assess and treat patients with SE rapidly. This trial has been designed to avoid delays of treatment of even just a few minutes because longer delays may increase morbidity or mortality. See section 5 of this protocol for an extensive discussion of the use of EFIC and related processes in this trial.

12.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (see template) and any subsequent modifications will be reviewed and approved by the IRB for each site responsible for oversight of the study.

12.2 Data and safety monitoring board (DSMB)

A Data and Safety Monitoring Board (DSMB) appointed by the NINDS will provide ongoing evaluation of safety data as well as the overall conduct of the trial. The DSMB will be formed by the NINDS as per institute guidelines. The SDMC statisticians will generate Data and Safety Monitoring (DSMB) Reports semi-annually or more frequently as needed. This review will aid in identifying any safety issues that may need to be addressed.

12.3 Subject Confidentiality

All data (case report forms, recordings, laboratory specimens, and other records) kept at the site will be physically and electronically secured to maintain subject confidentiality. Paper records and computers with subject data will be stored in locked office or cabinet. Computer records will always be password protected, and encrypted when possible. The study database is maintained behind a secure firewall, access is password protected and uses SSL encryption for all data entry and access. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the sponsor, the CCC, the SDMC. the IRB, the FDA, the NINDS, or the OHRP.

12.4 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

13. PUBLICATIONS AND DATA SHARING

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee, and all applicable regulations and rules including reporting to clinicaltrials.gov . Refer to the MoP for further detail.

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STUDY PROTOCOL

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.

Study Chair: Jaideep Kapur, MD, Professor, University of Virginia

Supported by: The National Institute of Neurological Disorders and Stroke (NINDS)
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ClinicalTrials.gov ID: NCT01960075

Sponsor of IND: Jaideep Kapur, IND 119,756

Version: 2 Final
previous version 22 December 2014

adapted for the NETT from the NIND phase III template at:
http://www.ninds.nih.gov/research/clinical_research/toolkit/protocoltemplate.htm

PROTOCOL CHANGES

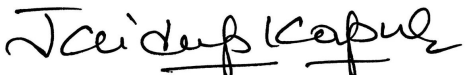
If amended versions of this protocol are required, this page will be populated with a specific log of all changes.

	Version 1		**Version 2**	
Section	**Page**	**Previous text**	**Page**	**New text**
	5		7-8	IN Intranasal PB Per Buccal PE Phenytoin Equivalents
Synopsis	11	subjects greater than or equal to 40 kg	13	all adults and those children greater than or equal to 32 kg
2.3	17	Pharmacokinetics, dose and rate of administration:	19	Pharmacokinetics, dose and rate of administration: By convention, FOS is dosed in phenytoin equivalents (PE). In this protocol, all FOS doses given in mg indicate mg PE whether explicitly stated or not.
4.1	27	...for those greater than or equal to 40 kg. For children less than 40 kg...	29	...for all adults and those children greater than or equal to 32 kg. For children less than 32 kg...
4.1	28	In Table 1. Those ≥ 40 kg	30	In Table 1. For all adults and those children ≥ 32 kg
4.1	28		30	In Table 1. For purposes of this study IO is considered equivalent to IV. For midazolam, IN or PB are considered equivalent to IM.
4.2	29	In Table 2. Opt-out identification	31	In Table 2. Opt-out identification or otherwise known to be previously enrolled in ESETT
7.2	42	... and flushing the line at the end of infusion ...	44	... and removing the line at the end of infusion ..
7.2	43	In Table 3. FOS mg	45	In Table 3. FOS mg PE
7.2	43	In Table 3. Subject Wt column shows lower end of each range	45	In Table 3. Subject Wt column now shows weight ranges on each row
7.4	44	...2-18 years, 19-65 years, ...	46	...less than 18 years, 18-65 years, ...
7.5	44	4-8 °C	46	2-8 °C
7.6	45	FOS 16.66 mg/ml....FOS 20 mg/kg	47	FOS 16.66 mg PE/ml....FOS 20 mg PE/kg

8.2	47	1. Contemporaneous direct data entry. If the primary outcome is directly entered into the CRF in WebDCU at the bedside, the CRF itself will be considered the primary source document. 2. Study book form worksheet. If a paper version of the CRF is used as a worksheet, that worksheet will be used to complete the CRF in WebDCU and must be maintained in the study binder and considered the primary source document. 3. Protocol Assist Device. The primary outcome recorded on the protocol assist device will be treated as a source document and may be used as an electronic CRF worksheet from which to complete the CRF. 4. Medical Record - study note template. The clinical medical record may also be the source document. A templated study note takes precedence among medical records. 5. Medical Record - adjudicated. If there is no structured source of the primary outcome, the medical record will be the source and the adjudicated primary outcome used.	49	1. Contemporaneous observation and documentation. The primary outcome is observed by the study team at the bedside and directly recorded on the CRF or on the study book worksheet. Direct data entry in WebDCU is preferred but not required. 2. Direct communication with the clinical team. The study obtains the primary outcome data by direct explicit communication with the treating ED attending physician. Communication should occur and be documented as close to the time of assessment as possible. 3. Protocol Assist Device. The primary outcome explicitly recorded on the protocol assist device will be treated as a source document and may be used to complete the CRF if contemporaneous recording or direct communication with the study team are not available. 4. Medical Record - explicit study specific documentation. If the medical record is used as a source document, the adjudicators will determine the primary outcome from an explicit study specific template note if available in precedence among available documentation. 5. Medical Record - implicit review. If the medical record is used as a source document, and no explicit study specific template note is available, the adjudicators will determine the primary outcome from their interpretation of provided documentation.
8.3	47	...Richmond agitation and sedation score (RASS) at 60 minutes,...		(duplicative listing deleted)
9.5	52	RASS	54	(erroneous bullet deleted)
10.2	53		55	Emergency unblinding performed prior to 60 minutes or prior to determination of the primary outcome, because of physician judgment that it is necessary for the safety or care of the patient, or because of unanticipated situations is accommodated by calling the hotline but is a deviation from this protocol.
14	62	REFERENCES	64	New section 14 INTEGRATED SUB-STUDIES has been added. REFERENCES is now section 15

PROTOCOL SIGNATURE PAGE

I have read the attached clinical protocol titled Established Status Epilepticus Treatment Trial (ESETT) Version 2, dated 24 October 2016. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.



24 October 2016

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Sponsor's Signature Date of Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described.

I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make all reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

_____

Investigator's Signature Date of Signature

CONTACT INFORMATION

For updated contact information, including the Emergency 24/7 Toll Free Contact Number, please refer to the study website ESETT.org or the study Manual of Procedures.

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TABLE OF ABBREVIATIONS

AE	Adverse Event
CCC	Clinical Coordinating Center
cEEG	Continuous Electroencephalogram Monitoring
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events Version 3.0
DCR	Data Clarification Request
DCU	Data Coordination Unit
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
ECG	Electrocardiogram
EEG	Electroencephalogram
EFIC	Exception from Informed Consent
EMS	Emergency Medical Services
ESE	Established Status Epilepticus
ESETT	Established Status Epilepticus Treatment Trial
ET	Endotracheal
FDA	Food and Drug Administration
FOS	Fosphenytoin
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IM	Intramuscular
IND	Investigational New Drug
IN	Intranasal
IO	Intraosseous
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LEV	Levetiracetam
mg	Milligram
Min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
MoP	Manual of Procedures
MM	Medical Safety Monitor
MUSC	Medical University of South Carolina
NETT	Neurological Emergencies Treatment Trials

NINDS	National Institute of Neurological Disorders and Stroke
PB	Per Buccal
PE	Phenytoin Equivalents
PECARN	Pediatric Emergency Care Applied Research Network
PGS	Purple Glove Syndrome
PHT	Phenytoin
PHTSE	Pre-hospital Treatment of Status Epilepticus Trial
PI	Principal Investigator
PR	Per Rectum
RAMPART	Rapid Anticonvulsant Medication Prior to Arrival Trial
RAR	Response Adaptive Randomization
RASS	Richmond Agitation and Sedation Score
RBC	Red Blood Cell
SAE	Serious Adverse Event
SDMC	Statistical & Data Management Center
SE	Status Epilepticus
SSL	Secure Socket Layer
SOP	Standard Operating Procedures
VAL	Valproic acid
WebDCU	Web-based Clinical Trial Management System

TABLE OF CONTENTS

SYNOPSIS

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.

Objectives: 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). The **second** objective is comparison of three drugs with respect to secondary outcomes. The final objective is to ensure that the trial is informative for treatment of established SE in children by describing the effectiveness, safety, and rate of adverse reactions of these drugs in children.

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. The following are **secondary outcomes**: occurrence of life threatening hypotension or cardiac arrhythmia, time to termination of seizures, intubation, admission to ICU, seizure recurrence, length of stay in the ICU and hospital, mortality, and Richmond agitation and sedation score at 60 minutes, will be compared between treatment groups.

Methods: This is a randomized, multicenter, Bayesian response adaptive comparative effectiveness trial of three active treatments in patients with status epilepticus who have failed treatment with benzodiazepines. Each subject will be followed until discharge or 30 days from enrollment, whichever comes first. This trial will be monitored for early success and futility.

Inclusion: Patients greater than or equal to 2 years of age, witnessed to have a clinically apparent seizure in the ED, 5-30 minutes after already having received at least an adequate dose of benzodiazepines for generalized, tonic-clonic convulsion(s). Adequate doses of benzodiazepines for this study are defined as: diazepam 10 mg IV, lorazepam 4 mg IV, or midazolam 10 mg IV or IM for all adults and those children greater than or equal to 32 kg, and diazepam 0.3mg/kg IV, lorazepam 0.1 mg/kg IV or midazolam 0.3mg/kg IM or 0.2 mg/kg IV for those children less than 32 kg. These drugs may have been administered in two or more divided doses, including in the out-of-hospital setting.

Interventions and Duration: The required concentrations of the study drugs (FOS 16.66 mg/ml, VPA 33.33 mg/ml and LEV 50 mg/ml) will be produced, packaged and labeled by the University of California at Davis Good Manufacturing Practice (GMP) facility and shipped to the study sites. The study drugs are identical in appearance, formulation, packaging, and administration

(including volume and rate of infusion). The assigned treatment dose (FOS 20 mg/kg, LEV 60 mg/kg or VPA 40 mg/kg) will be infused over 10 minutes. The study participants will be observed for 20 minutes, while the duration of clinical seizures and response to verbal or painful stimuli is recorded. At 60 minutes from start of study drug infusion, the primary outcome is determined.

Randomization: Any patient witnessed to have seizures in the emergency department (ED) will be evaluated for enrollment based on inclusion and exclusion criteria. Enrollment will occur under exception from informed consent rules (EFIC) due to the emergent and life-threatening nature of SE. This is an intent-to-treat study so all subjects randomized will be included in the primary analysis. Time of randomization is the time when the infusion pump, connected to study drug vial and patient's IV catheter, is switched on. The randomization scheme will be equal allocation (1:1:1) for the first 300 patients. Once 300 subjects are randomized, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm.

Interim Analyses: Interim monitoring for success and futility will begin after 400 subjects have been enrolled and will be repeated after every additional 100 subjects are enrolled . This trial will stop early for success if the analysis identifies the maximum effective treatment with at least 97.5% probability.

Sample Size: This study will randomize a maximum target of 795 subjects over 4 years, at an accrual rate of approximately 16.5 subjects per month. This sample size provides approximately 90% power to identify the most effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (an absolute difference of 15%). A 15% difference is the minimum clinically important difference sufficient to change clinical practice. The trial operating characteristics for this adaptive design were determined via an extensive simulation study, which ensures the type I error probability is less than 0.05 under a variety of scenarios.[37]

Participating Sites: Patients will be recruited by two national emergency research networks: Neurological Emergencies Treatment Trials (NETT) network and Pediatric Emergency Care Applied Research Network (PECARN). Each network has successfully participated in SE treatment trials in compliance with EFIC regulations.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to determine the most effective and/or the least effective treatment (between fosphenytoin, levetiracetam and valproic acid) of benzodiazepine-refractory SE among patients greater than or equal to 2 years. 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.

1.2 Secondary Objectives

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

2. BACKGROUND

2.1 Rationale

SE is defined as a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness between seizures (Lowenstein 1999). Epidemiological studies carried out in Richmond, VA, found an annual incidence of SE ranging from 41/100,000-61/100,000 (DeLorenzo 1996). Based on these studies, there are approximately 120,000-180,000 episodes of convulsive SE each year in the US. SE affects individuals of all ages from the very young to the elderly. It complicates many neurological and systemic illnesses. The mortality associated with SE is estimated as 17%. SE also leads to morbidity including cognitive defects and neurological injury. The morbidity and mortality of SE is determined by the underlying cause of the SE and the length of time in SE (Neligan 2010; Towne 1994). The Febrile status epilepticus study (FEBSTAT) suggests that SE, but not individual seizures, injures the hippocampus (Nordli, 2012; Shinnar 2012). Early termination of SE can limit development of refractory SE, neurological injury and mortality in experimental animals (Fujikawa 2005; Kapur 1997). SE is particularly common in children (Shinnar . 1997). Although multiple different etiologies such as infection, tumors, fever, preexisting neurological injury or brain malformation cause SE, the primary goal of treatment is prompt termination of seizures because adverse consequences of SE increase with seizure duration (Chen 2007; Lothman 1990; Meldrum 1973; Meldrum 1986).

SE is initially treated with benzodiazepines. This selection is based on three double-blind, randomized, controlled clinical trials (Alldredge 2001; Treiman 1998, SIlbergleit 2012). In the VA Cooperative Study (Treiman 1998), intravenous lorazepam was found to be superior to phenytoin. In the Pre-hospital Treatment of Status Epilepticus (PHTSE) study (Alldredge 2001), lorazepam and diazepam were found to be superior to placebo. In these studies, lorazepam was effective in terminating SE in 55-65% of patients. The recently published RAMPART study compared intramuscular midazolam to intravenous lorazepam for the initial treatment of SE (Silbergleit 2012). It concluded that intramuscular midazolam is at least as safe and effective as intravenous lorazepam for patients in convulsive status epilepticus (Silbergleit 2012). Benzodiazepines are also the first treatment of choice in children (Loddenkemper 2011). The recently published Pediatric Seizure Study found that lorazepam was not superior to diazepam for pediatric SE (Chamberlain 2014). Unfortunately, approximately 35-45% of patients are refractory to benzodiazepines. Benzodiazepine-refractory SE is also called established SE. ESETT is a clinical trial testing the relative efficacy and safety of three treatments in patients who do not respond to benzodiazepine treatment (Cock 2011; Prasad 2005). The need for such a trial has been emphasized in review articles, guidelines and by experts in the field (Lowenstein 2005;Meierkord 2010; Wheless 2008).

For the purpose of this trial, “established SE (ESE)” is defined as an episode of generalized convulsive SE in which seizure activity continues despite administration of adequate doses of

benzodiazepines. It has long been recognized that SE is a dynamic and rapidly evolving condition which eventually becomes self-sustaining (Lothman 1990; Lothman 1989; Treiman 1990; VanLandingham 1991a; VanLandingham 1991b). Ongoing seizures rapidly modify neuronal activity and synaptic function (Chen 2007; Macdonald 1999). This rapid neuronal plasticity is manifested in changes in seizure behavior, EEG patterns, sensitivity to drugs, and evolution of neuronal injury and death. EEGs recorded from patients soon after onset of generalized convulsive SE demonstrate discrete seizures interspersed with normal activity, which evolves to continuous waxing and waning spike–wave discharges (Treiman 1990). Benzodiazepines given soon after the onset of generalized convulsive status epilepticus are effective in terminating seizures in 60-72% of patients. As time passes, these drugs become far less effective, terminating seizures in less than 25% of patients (Treiman 1998).

Benzodiazepines act on GABA-A receptors and enhance inhibitory synaptic transmission (Goodkin 2009). In experimental animals, benzodiazepines terminate seizures effectively if they are given soon after the start of seizures--when EEG demonstrates recurrent seizures and behavioral seizures are mild. Benzodiazepines are less effective in treating longer lasting SE, especially after electrographic seizures have merged and 10 or more minutes have elapsed since first generalized tonic-clonic seizure (Jones 2002; Kapur 1997; Walton 1988; Wang 2009). Studies further reveal that inhibitory synaptic transmission mediated by GABA-A receptors is reduced in the hippocampi of animals in ESE (Goodkin 2008; Kapur 1995; Kapur 1997; Naylor 2005; Terunuma 2008). Biochemical studies reveal a decrease in the number of functional receptors on the post-synaptic membrane in the hippocampi of animals in established SE (Goodkin 2005; Goodkin 2008; Naylor 2005; Terunuma 2008). This rapid receptor plasticity is believed to be mediated by prolonged seizures, which activate many second messenger pathways (Brunig 2001; Pal 2001). In summary, prolonged seizures modify GABA-A receptors and lead to ESE.

Further treatment should ideally focus on mechanisms other than GABA-A receptors, such as sodium channels, calcium channels, or glutamatergic transmission. Currently, there are several drugs available in the intravenous formulation that can modify these systems. Lacosamide and FOS modify sodium channels. LEV modifies glutamatergic synaptic transmission by binding to the synaptic vesicle proteins. VPA has multiple actions on several neurotransmitter systems and ion channels. These mechanisms are described in the respective package inserts.

2.2 Study Drugs

The primary goal of treatment of ESE is to terminate seizures rapidly, without causing respiratory or cardiovascular compromise, or coma. The active form of the drug must enter the brain rapidly, access its target and stop ESE. Three drugs were selected for this study based on

current recommendations of professional groups, current clinical practice, and safety and efficacy data.

Recently, the Status Epilepticus Guideline Writing Committee of the Neurocritical Care Society (NCS) reviewed current evidence and classified it according to American Heart Association/American College of Cardiology guidelines for evidence rating (Brophy 2012). The Neurocritical Care Society rated common anticonvulsants for the treatment of SE as follows:

VPA: Class IIa, level A—weight of evidence/opinion is in favor of usefulness/efficacy based on data derived from multiple randomized clinical trials.

FOS: Class IIa, level B--weight of evidence/opinion is in favor of usefulness/efficacy based on data derived from a single randomized trial or nonrandomized trials.

LEV: Class IIb, level C--weight of evidence/opinion is in favor of usefulness/efficacy based on consensus opinion of experts.

These three medications are sometimes referred to by certain brand names. Fosphenytoin may referred to as Cerebyx or, inaccurately, as Dilantin, the brand name of the active metabolite of this pro-drug. Levetiracetam may be referred to as Keppra. Valproic acid may be referred to as Depacon or Depakote.

The NCS guidelines recommended use of either FOS or VPA for the treatment of established SE (Brophy 2012).

To identify current practice, a critical care pharmacy group studied the patterns of anticonvulsant use for benzodiazepine refractory status epilepticus in the neurocritical care units. This survey analyzed the medical records of 10-20 recent SE patients from the critical care units at 15 academic medical centers. Among the 150 patients studied, benzodiazepines were the most commonly used first agent (75%) for treatment of SE. FOS was the most commonly used second anticonvulsant (33%). LEV was less commonly used (10%) and VPA was rarely used (<2 %) (Cook 2012). The NCS Status Epilepticus Guideline Writing Committee reported the preferences of 50 identified experts among neurointensivists, neurologists and epileptologists for the treatment of ESE. Among the respondents for this survey, 80% chose FOS (or phenytoin), 6% chose LEV and 2% chose VPA (Riviello 2006). In a survey of 21 pediatric ED directors from the Pediatric Emergency Care Applied Research Network (PECARN), FOS was the most commonly used treatment for ESE in pediatric patients followed by LEV, phenobarbital, and VPA.

Intravenous formulations are available for FOS, LEV, VPA, lacosamide and phenobarbital. Of these drugs, phenobarbital causes sedation and respiratory depression, especially in those who have been treated with benzodiazepines. This side effect limits the popularity of phenobarbital

as a second line agent for SE. The safety of rapid intravenous administration of lacosamide has been established in adults but not in children (Fountain 2012). Children constitute a large fraction of patients with SE. Three hundred thirty-six of approximately 795 of subjects to be randomized into this study will be children. There are limited data on the efficacy of lacosamide in established SE, especially in children. For these reasons, lacosamide and phenobarbital were not included in the study.

2.3 FOS (fosphenytoin)

FOS is the most commonly recommended treatment for ESE in many current treatment guidelines (Brophy 2012; Loddenkemper 2011; Meierkord 2010) and is generally considered the standard of care. In a survey of critical care neurologists published in 2003, 95% of responders (n= 106) used FOS or phenytoin for the treatment of ESE (Claassen 2003). Two more recent surveys suggest that it is currently the most commonly used drug for the treatment of ESE in the US (Cook 2012; Riviello 2012). A survey of pediatric ED physicians belonging to the Pediatric Emergency Care Action Research Network (PECARN) reported that the majority of physicians treating children use FOS for the treatment of ESE.

Pharmacokinetics, dose and rate of administration: By convention, FOS is dosed in phenytoin equivalents (PE). In this protocol, all FOS doses given in mg indicate mg PE whether explicitly stated or not. In order to achieve rapid termination of seizures, drugs need to be administered rapidly. Drugs are delivered over a 10 minute infusion period in ESETT. FOS can be administered at a maximum rate of 150 mg/min in order to avoid hypotension and cardiac arrhythmias (see boxed warning, package insert). This limits the maximum dose of the drug that can be administered safely over 10 minutes to 1500 mg. The recommended loading dose of FOS is 18-20 mg/kg. Therefore, patients weighing less than 75 kg will receive a loading dose 20 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 1500 mg over 10 minutes. Because more than 65% of adult men and 45% of adult women weigh more than 75 kg, weight-based dosing will typically apply to children and fixed dosing to adults. This dosing regimen is consistent with current recommendation for the use of anticonvulsants, where children are dosed on a mg/kg basis while adults are given fixed doses (see package insert phenytoin, LEV, and VPA). In general, children are given larger doses of anticonvulsants because of differences in the pharmacokinetics.

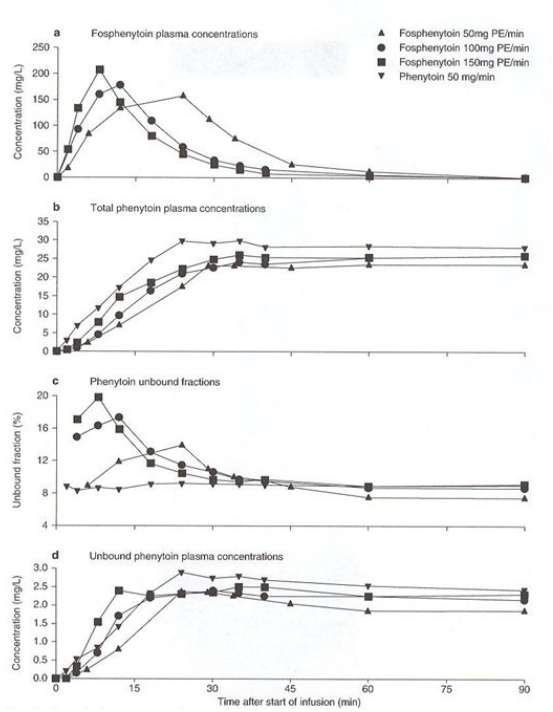

Figure 1. (Fischer 2003)

The pharmacokinetics of FOS (1200 mg) administered at the rate of 150 mg phenytoin equivalents (PE)/min is illustrated in Figure 1 (Fischer 2003). Most clinically relevant is panel d showing unbound (free) phenytoin plasma concentrations following administration. These remain in 2.0- 3.0 mg/L range 90 minutes after administration. The accepted therapeutic range of unbound plasma concentration is 1 to 2 mg/L. Patients receiving a single dose of FOS (1500 mg) are expected to maintain a free phenytoin concentration above 2 mg/L for 90 to 120 minutes. It is thus reasonable in the patient who has stopped seizing to wait for 2 hours from start of infusion to start or restart anticonvulsant medication.

FOS is a prodrug which must be converted to phenytoin (PHT) to exert its action (Walton 1990). FOS has to undergo dephosphorylation before it can enter the brain. Figure 2 illustrates the rate of accumulation of PHT in rat plasma and brain after single intraperitoneal injection of FOS (called ACC 9653 at the time of publication) or PHT (Walton 1990). Note that peak plasma PHT concentration was achieved 30 minutes after FOS injection. The peak brain PHT level was attained 60 minutes after administration. PHT is effective against partial onset seizures and secondarily generalized seizures, but its efficacy in primary generalized seizures is not established. It exerts its anticonvulsant action by stabilizing the inactivated state of sodium channels (Macdonald 1994). FOS gets converted into phenytoin and enters the brain. FOS can be administered faster than phenytoin.

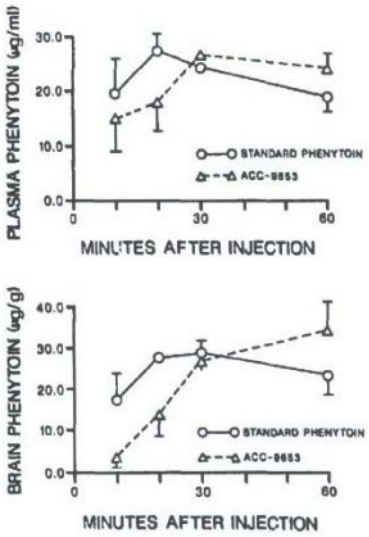

Fig. 1. Phenytoin concentrations in plasma (upper figure) and brain (lower figure) following i.p. injection of 130 mg/kg ACC-9653 or 120 mg/kg standard phenytoin. Each point is the mean ± standard error for 3 rats.

Figure 2. (Walton 1990)

Safety: According to the package insert, the dose of IV FOS (15 to 20 mg PE/kg) that is used to treat status epilepticus is administered at a maximum rate of 150 mg PE/min to avoid cardiovascular side effects. Hypotension may occur, especially after IV administration at high doses and high rates of administration. Severe cardiovascular reactions and fatalities, such as atrial and ventricular conduction depression and ventricular fibrillation, have been reported following PHT administration, especially in elderly or gravely ill patients. These complications are less frequent with FOS, but careful cardiac monitoring is still needed when administering IV loading doses of FOS. Reduction in rate of administration or discontinuation of dosing may be necessary. This ESETT protocol calls for these reductions if needed while administering the study drug.

Rash: Exfoliative, purpuric, or bullous, rashes, Stevens-Johnson syndrome, or toxic epidermal necrolysis are known to occur with chronic administration of PHT.

Hepatotoxicity: Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes.

Hemopoietic system: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and

pancytopenia with or without bone marrow suppression have been reported.

Prenatal exposure to phenytoin was not found to have additional significant clinical risk in a recent Cochrane meta-analysis (Bromley 2014). Theoretical risks are related to prolonged exposures rather than single dose exposures as in this trial. Theoretical risks include congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. Patients known to be pregnant will be excluded from this trial anyway as per the secretarial waiver allowing studies with EFIC.

Efficacy in animal studies: Fosphenytoin and PHT are not effective in termination of benzodiazepine refractory SE in animal model ESE. In an electrical stimulation model where excitatory inputs to the hippocampus were stimulated (perforant path) for 60 minutes, the resulting in-animal model ESE was not terminated by phenytoin (50 mg/kg) given intravenously (Mazarati 1998). In another animal model of ESE based on electrical stimulation of the hippocampus for 90 minutes, phenytoin did not suppress seizures (Prasad 2002). Finally, in a cholinergic stimulation (nerve agent-induced) animal model ESE, FOS had little or no therapeutic effect either administered alone or in combination with diazepam (McDonough 2004).

Efficacy in open studies: In open-label studies for initial treatment of SE, the reported efficacy of PHT in terminating SE ranges from 44-88% (Trinka 2009). In the VA Cooperative study (Treiman 1998), PHT was effective in initial treatment of convulsive SE in 42% of patients, but in only 7.7 % patients with subtle SE. Effectiveness in ESE was not studied. A systematic, retrospective analysis concluded that phenytoin was effective in 58.6% of patients with SE who did not respond to benzodiazepines (Alvarez 2011).

2.4 LEV (levetiracetam)

Recently published guidelines for the treatment of ESE in adults and children recommend LEV as an alternative to FOS (Brophy 2012; Loddenkemper 2011; Meierkord 2010). In surveys of experts and pediatric ED physicians, LEV is the second most commonly used drug for the treatment of ESE in neurological intensive care units (Cook 2012; Riviello 2012). It is used for the treatment of partial and generalized tonic-clonic seizures, myoclonic seizures and seizures associated with juvenile myoclonic epilepsy. It binds to synaptic vesicle protein 2 (SV2) and modulates neurotransmission. An intravenous formulation of the drug has been available for several years and it is labelled for use when patients cannot swallow or for initiating therapy for

seizure.

Pharmacokinetics & safety: Doheny et al investigated the plasma and brain concentrations of LEV after bolus intraperitoneal injection of 20, 40 or 80 mg/kg of the drug to rats. Serum LEV concentration increases and peaks rapidly, but brain accumulation is slow and peaks 90-100 minutes after administration (Doheny 1999).

Dose and rate of administration: The recommended LEV dose in children up to 40 kg is 20-60 mg/kg per day (package insert). In adults, the recommended dose range is 1-3 g per day, but higher doses up to 6 g per day are commonly used. The safety of rapid intravenous administration of LEV has been assessed. Intravenous doses of 2500 mg have been administered over 5 minutes and doses of 4000 mg have been given over 15 minutes safely in adults (Ramael 2006a). The common adverse effects in these patients were dizziness, somnolence, irritability and headache (Ramael 2006a). Based on these considerations, subjects weighing up to 75 kg will receive a loading dose 60 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 4500 mg over 10 minutes.

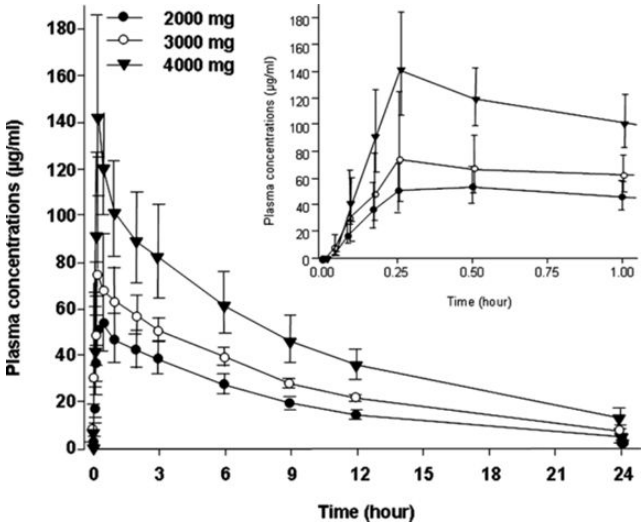

Figure 3. (Ramael 2006b)

Figure 3 demonstrates the pharmacokinetics of LEV following injection of 2000, 3000 or 4000 mg of the drug (Ramael 2006b). It is noteworthy that within 15 minutes of injection the plasma concentration of LEV peaks and remains above 40 µg /ml for 9 hours. The therapeutic concentration of LEV is considered to be 12 to 46 µg /ml. Therefore, patients treated with LEV are likely to have therapeutic concentrations of the drug for 8 to 10 hours after the start of infusion.

Safety: Suicidal ideation: Chronic administration of LEV increases the risk of suicidal thoughts or behavior. Patients treated with LEV for should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Risk of suicidal ideation associated with a single dose of LEV is unknown.

CNS: CNS effects include somnolence and fatigue, coordination difficulties, and behavioral abnormalities observed in pediatric and adult population.

Hematopoietic: Minor, but statistically significant, decreases in total mean RBC count (0.03 x 106/mm3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in LEV-treated adult and pediatric patients in placebo-controlled trials.

Pregnancy Risks: The best available evidence is that there are no risks related to pregnancy from the administration of levetiracetam in humans. Current data suggests that the overall risk of major malformation after first trimester exposure to levetiracetam is within the population baseline risk of 1-3%, with no apparent adverse effects on long term child development. The effect of a single dose of LEV has not been studied, but would be of lower risk than repeated dosing (Chaudhry SA, 2014, Bromley 2014).

Efficacy in animal model ESE: LEV administered alone reduced the duration of perforant path stimulation–induced animal ESE (Mazarati 2004). When used in combination with diazepam, low doses of LEV rapidly terminated behavioral and EEG seizures (Mazarati 2004). In the cholinergic stimulation animal model of ESE, LEV administered alone suppressed behavioral seizures, but EEG seizures continued unabated (Zheng 2010).

Efficacy in open studies: Although no randomized controlled clinical trial for this agent has been performed, a large number of open case series and reports have been published. An analysis of publications until 2009 reported that 707 patients with various forms of SE had been treated with LEV. The success rate was about 70% (Trinka 2011). In ESE, the efficacy of LEV is reported as 51.7 % in one study (Alvarez 2011) and 73.2% in another study (Tripathi 2010).

2.5 VPA (valproic acid)

VPA was recommended for the treatment of ESE in recent guidelines (Brophy 2012; Meierkord 2010). In surveys, VPA is the third or 4th most commonly used drug for the treatment of ESE in the U.S. (Cook 2012; Riviello 2012). VPA is an anticonvulsant commonly used for the treatment of primary generalized seizures, myoclonic seizures and focal seizures. The drug has multiple actions on the GABA neurotransmitter system and calcium channels (Macdonald 1995). Valproate sodium is the salt of the valproate ion which is synonymous with VPA.

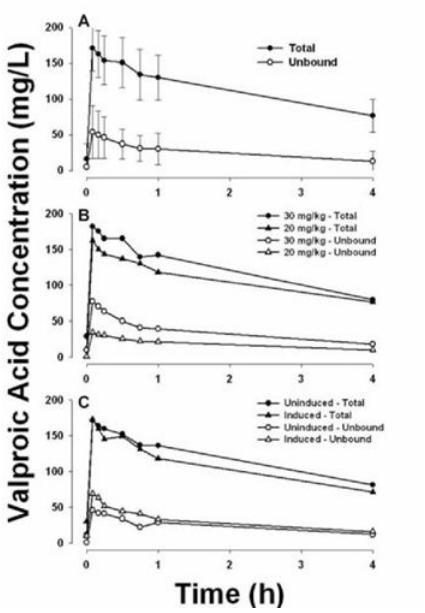

Figure 4. (Limdi 2007)

Pharmacokinetics: Subjects weighing up to 75 kg will receive a loading dose of 40 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 3000 mg over 10 minutes. Based on published pharmacokinetic data (Limdi 2007), serum VPA levels will peak between 150-200 mg/L within minutes of administration and then remain in the 50-150 mg/L range for the next 4 hours (see Figure 4). Pharmacokinetics of IV VPA has been studied in children with epilepsy (Birnbaum 2003; Panomvana Na 2006; Ramsay 2003; Visudtibhan 2011; Williams 2012). Recent studies suggest that the pharmacokinetics of rapid intravenously administered VPA conforms to models developed using oral VPA in children and oral and intravenous VPA in adults (Williams 2012). Intravenous VPA is safe in acutely ill children with recurrent seizures and in those with epilepsy (Birnbaum 2003; Ramsay 2003).

Dose and rate of administration: Recommended VPA dose ranges from 15-45 mg/kg/day. VPA has been administered rapidly by the intravenous route. In one study it was administered at the rate of up to 10 mg/kg/minute for doses up to 30 mg/kg (Limdi 2005). In another study in children it was given at rates up to 11 mg/kg/min for dose up to 40 mg/kg (Venkataraman 1999; Wheless 2004). The most common adverse events were injection site pain, pain with infusion, dizziness, and somnolence. Based on these considerations, subjects weighing up to 75 kg will receive a loading dose of 40 mg/kg over 10 minutes. Those weighing 75 kg or more will receive a fixed dose of 3000 mg over 10 minutes.

Safety in pregnant women Children born to mothers taking long durations of high doses of VPA during pregnancy may have a higher than expected incidence of reduced cognitive performance at ages 3 and 4.5 (McVearry 2009; Meador 2009; Werler 2011). These risks are dose dependent and vary across studies. They have only been found to be are associated with chronic administration of VPA (Bromley 2014). There is no evidence that a single dose of VPA

given during pregnancy can cause birth defects.

In a series of reviews of hepatotoxicity associated with VPA, Dreifuss and colleagues concluded that the primary risk of fatal hepatic dysfunction (1/500) was found in children 0 to 2 years old receiving VPA as polytherapy. The risk declined with age and was low in patients receiving VPA as monotherapy (1/37,000). No hepatic fatalities occurred in patients above the age of 10 years receiving VPA as monotherapy (Bryant 1996; Dreifuss 1987; Dreifuss 1989). There are reports that polymerase c gene (POLG) determines the risk of VPA -induced hepatotoxicity (Stewart 2010). However, the POLG polymorphisms were discovered in patients who had been chronically treated with VPA and had elevated hepatic enzymes. The authors concluded that the genetic variants reduced the regenerative capacity of the hepatocytes following injury. Patients with mutations in POLG have metabolic encephalopathy. There is no report of hepatotoxicity associated with a single dose of VPA. Patients below age 2, and those with known or suspected metabolic encephalopathy are excluded from ESETT.

Exclusion of patients known to be pregnant, younger than 2 years and with known or suspected metabolic encephalopathy will reduce the possibility of VPA exposure to the population at risk for toxicity. There is a small risk that a pregnant patient who is not identified as pregnant by history or physical examination will be included in the study. The risk of toxicity is mitigated by the fact that a single dose of VPA will be used. This risk should be weighed against the known morbidity and mortality of ESE and compared to the risk of administering FOS.

Clinical studies: VPA has been used for the treatment of SE in prospective or retrospective series and two randomized open trials (Trinka 2009). An analysis of these trials reported that 693 adults or children in SE have been treated with VPA and the response rate ranging from 60-83% of patients. A pilot prospective randomized open study reported a trend towards superiority of VPA to phenytoin in treatment of SE (Misra 2006). Another study reported that VPA controlled SE refractory to PHT (Agarwal 2007).

2.6 Systematic comparison of FOS, VPA, and LEV for the treatment of ESE

There is one systematic study of treatment of ESE (Alvarez 2011). In a retrospective analysis of protocol-driven treatment of ESE, 279 adult episodes of SE were identified prospectively in which either PHT or VPA or LEV was given in a non-randomized un-blinded fashion after benzodiazepines failed (labeled Alvarez in figure 5 below). VPA failed to control SE in 25.4%, PHT in 41.4% and LEV in 48.3% of episodes. Because patients were not balanced with regards to etiology and severity of SE, a post-hoc adjustment for severity and etiology was performed. After this adjustment the authors reported that LEV failed more often than VPA (Odds ratio (OR) 2.69: 95% confidence interval 1.16-6.08)). PHT was not significantly different from the other two compounds. The authors concluded that LEV is less effective than VPA for control of

ESE and called for a prospective randomized trial of these agents.

Two ESE treatment studies were open-label, randomized, prospective studies. In the first study (labeled Agarwal on figure 5), one hundred patients aged two or older who had failed IV diazepam were randomized to either 20 mg/kg of VPA or 20 mg/kg of PHT. SE was controlled in 44 (88%) patients treated with VPA and 42 (81%) patients treated with PHT (Agarwal 2007). No significant difference was found between VPA and PHT in this open-labeled study. In the second study (Tripathi 2010) patients were randomized to IV LEV or IV VPA after failing diazepam treatment of SE. Status epilepticus was terminated by IV LEV in 30 patients and by IV VPA in 28 patients. In this study as well, there was no significant difference between LEV and VPA. In summary, one large head-to-head comparison of these three agents raised the possibility that VPA is superior to LEV for the treatment of ESE. The other studies were inconclusive. Expert evaluation of the published data suggests that VPA (Class IIa level A) may be superior to FOS (Class IIa level B), which may be superior to LEV (class IIb level C).

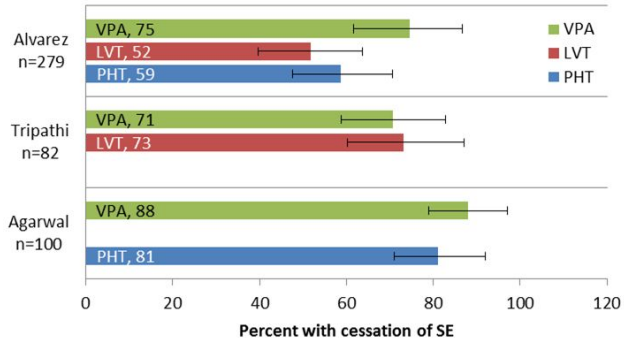

Figure 5. (Agarwal 2007, Alvarez 2011, Tripathi 2010)

In summary, current practice is to treat ESE with FOS or LEV. However no randomized controlled trials have demonstrated their efficacy in terminating ESE. Non-randomized and pilot studies suggest VPA may be more efficacious than LEV. Most expert ED physicians, neurologists, neuro-intensivists and pediatric neurologists believe that the next logical step is a randomized, blinded comparative efficacy study to decide the best treatment for ESE (Brophy 2012; Cock 2011; Loddenkemper 2011; Shorvon 2011; Trinka 2009).

3. STUDY DESIGN

This is a multicenter, randomized, Bayesian response-adaptive comparative effectiveness trial of three active treatments in patients with established SE who have failed treatment with benzodiazepines. Subjects will initially be randomized in a 1:1:1 ratio. Once 300 subjects are randomized, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm. Interim analyses are planned after 400, 500, 600, and 700 subjects are enrolled. At each interim analysis, there may be updates to the randomization probabilities. At each interim analysis, the trial may stop early for success or futility. The maximum approximate sample size is 795 subjects total.

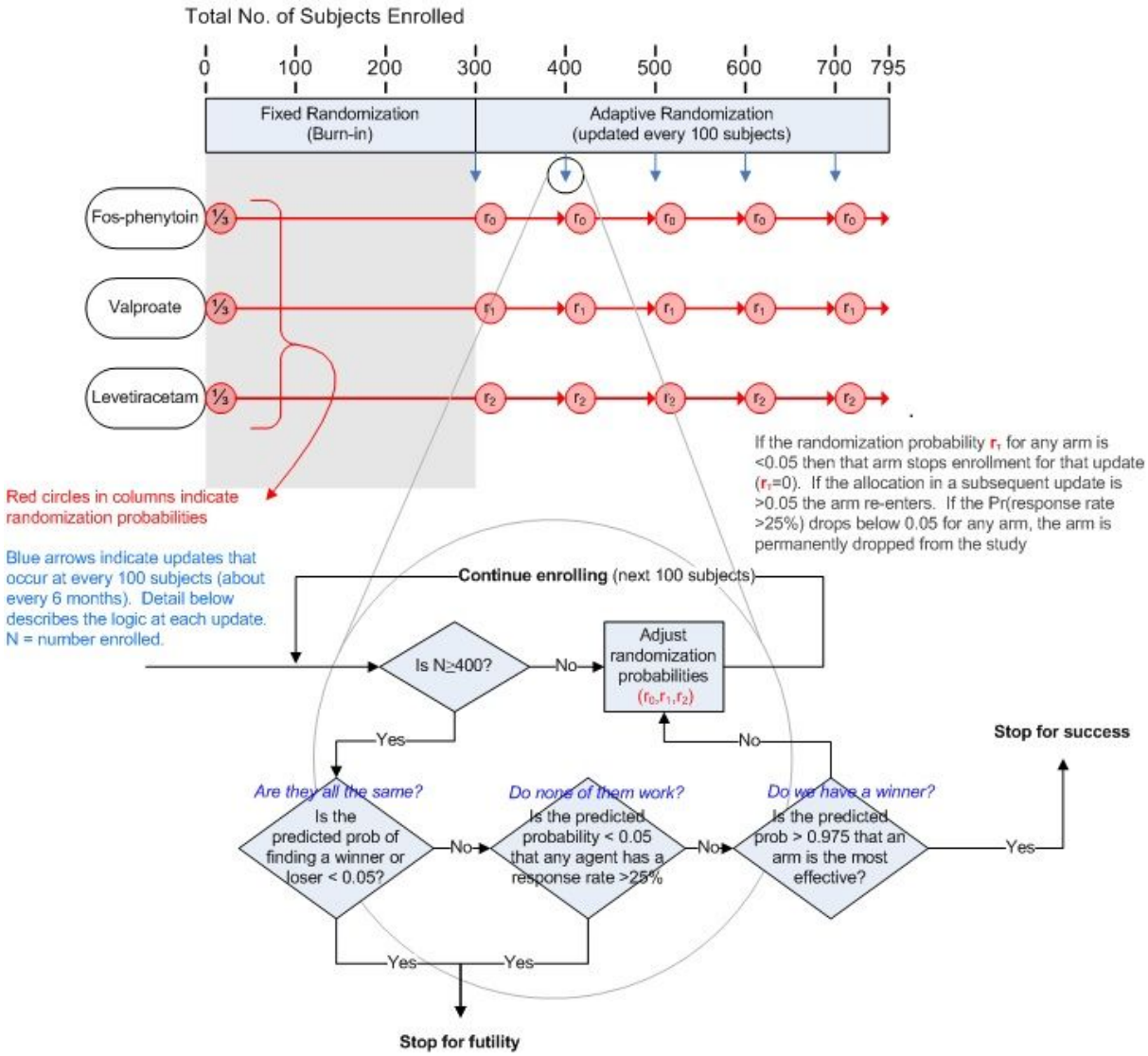

Figure 6.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

Patients will be included in this study if they are aged 2 or older, have been treated for generalized convulsive seizure of greater than 5 minutes duration with adequate doses of benzodiazepines, and who continue to have persistent or recurrent convulsions in the emergency department at least 5 minutes and no more than 30 minutes after the last dose of benzodiazepine. The inclusion criteria is intended to describe the population of patients for whom progression to second line anticonvulsants are indicated. The seizure and its initial treatment may have occurred prior to arrival in the ED.

Adequate doses of benzodiazepines for this study are determined to be: diazepam 10 mg IV, lorazepam 4 mg IV or midazolam 10 mg IV or IM for all adults and those children greater than or equal to 32 kg. For children less than 32 kg adequate doses are: diazepam 0.3 mg/kg IV, lorazepam 0.1 mg/kg IV and midazolam 0.3mg/kg IM or 0.2 mg/kg IV. These drugs may have been administered in two or more divided doses. The last dose of benzodiazepine must be given at least 5 minutes prior study drug initiation to provide this dose sufficient time to act. The last dose of benzodiazepine must be given within 30 minutes of study drug initiation to avoid enrolling patients in whom re-dosing of benzodiazepines may be more appropriate. Transmucosal benzodiazepines such as rectal diazepam or buccal midazolam given at home prior to EMS arrival may be included in the calculation of the cumulative adequate benzodiazepine dose, but at least one dose of benzodiazepines must be also given by EMS or in the ED between 5 and 30 minutes of study drug administration. There is no maximum dose of benzodiazepines imposed by this trial. Although these doses are considered the minimum adequate doses based on common clinical practice, it is recommended that the best practice (subject to local standards of care) is to administer 20 mg of diazepam, 8 mg of lorazepam, or 20 mg of midazolam in adults prior to progression to enrollment.

Table 1. Inclusion criteria and rationale

Inclusion criteria	Measure	Rationale
Patient witnessed to seize for greater than 5 minute duration prior to treatment with study drug	Witness or EMS report or clinical observation	PHTSE and RAMPART study suggest that the treatment of SE should begin when single seizure or recurrent seizures without recovery of consciousness have lasted more than 5 minutes.
Patient received adequate dose of benzodiazepines. The last dose of a benzo was administered in the 5-30 minutes prior to study drug administration. The doses may be divided.	EMS or ED record of treatment: For all adults and those children ≥ 32 kg adequate doses are: diazepam 10 mg IV or PR, or lorazepam 4 mg IV, or midazolam 10 mg IM or IV. For children <32 kg adequate doses are: diazepam 0.3 mg/kg IV or PR, or lorazepam 0.1 mg/kg IV, or midazolam 0.3mg/kg IM - 0.2 mg/kg IV For purposes of this study, IO is considered equivalent to IV. For midazolam, IN or PB are considered equivalent to IM.	According to current treatment guidelines initial therapy for SE is appropriate doses of these drugs. The 5 to 30 minute window is intended to provide the last dose sufficient time to act and to avoid enrolling patients in whom the last dose may have already worn off.
Continued or recurring seizure in the Emergency Department	Clinical observation	When patient fails to respond to adequate doses of benzodiazepines, a second line agent is needed to terminate SE.
Age 2 years or older	Caretakers report of age or clinical observation	The causes and treatment of SE in patients less than 2 years of age are different from those in older children and adults.

4.2 Exclusion Criteria

ESETT is intended to be broadly inclusive of the target population. The purpose of the exclusion criteria to prevent enrollment for three narrow categories of patients: those who can or should not be enrolled under EFIC, those who have already received confounding therapy, and those with medical contraindications to the study drugs or an indication for alternative treatment. Specific contraindications are listed and explained in table 2.

Table 2. Exclusion criteria and rationale

Criteria	Measure	Rationale
Known pregnancy	History and physical exam*	Pregnant women are excluded from studies performed under exception from informed consent (EFIC).
Prisoner	Look for prison guards	Prisoners are excluded from studies performed under exception from informed consent (EFIC).
Opt-out identification or otherwise known to be previously enrolled in ESETT	Look for medical-alert jewelry, bracelets, or trial-specific wrist bands labelled with "ESETT declined"	Provides a mechanism for those who wish to identify themselves prospectively to opt out of EFIC, or to identify and exclude cooperative potential re-enrollers.
Treatment with a second line anticonvulsant (FOS, PHT, VPA, LEV, phenobarbital or other agents defined in the MoP) for this episode of SE	Medication administration record	The use of any second line agents prior to enrollment in the study would confound determination of the effects of the study drugs.
Treatment with sedatives with anticonvulsant properties other than benzodiazepines (propofol, etomidate, ketamine or other agents defined in the MoP)	Medication administration record	Anticonvulsant sedative drugs are used for sedation and rapid sequence intubation. These drugs could terminate SE and would confound the primary efficacy outcome.
Endotracheal Intubation	History and examination	Prevents evaluation of patient for responsiveness.
Acute traumatic brain injury	Clinical history, evidence of head trauma	Other care, often requiring sedation, takes precedence.
Known metabolic disorder	Clinical history*	Patients with metabolic disorders are at risk for

		liver failure when treated with VPA (VPA package insert).
Known liver disease	Clinical history*	Patients with liver disease are at risk for liver failure when treated with VPA (VPA package insert)
Known severe renal impairment	Clinical history*	Severe renal impairment has been associated with reduced plasma protein binding of valproic acid and fosphenytoin, resulting in substantially elevated free concentrations of these drugs
Known allergy or other known contraindication to FOS, PHT, LEV, or VPA	Clinical history	As per package inserts for FOS, LEV, and VPA.
Hypoglycemia < 50 mg/dL	Finger-stick glucose	SE due to hypoglycemia is first treated by giving glucose and correcting it.
Hyperglycemia > 400 mg/dL	Finger-stick glucose	SE due to hyperglycemia is first treated by reducing glucose and correcting it.
Cardiac arrest / post-anoxic seizures	History and ECG rhythm strip	Prognosis of SE due to anoxia and cardiac arrest is uniformly poor and distinct from other causes.

* Laboratory testing is not indicated to screen for these exclusion criteria because the risk of delay in treatment is much greater than the risk enrollment with these conditions.

5. Informed Consent and Exception from Informed Consent (EFIC)

Respect for human subjects and their safety are paramount in this trial. Research involving subjects who have SE, however, presents an ethical challenge. Protecting patient autonomy through the informed consent process is typically an ethical cornerstone of human subjects research, but because patients in generalized SE are unconscious, an informed consent process is not possible and patients cannot say whether or not they would want to participate in the research. Furthermore the alternative process of identifying and obtaining surrogate informed consent from a legally authorized representative (LAR) is not practicable in SE, because the emergency treatment being studied must be initiated as quickly as possible to safely care for the patient. Identification of the optimal emergency care for those in SE in this trial can therefore only be conducted with exception from informed consent (EFIC) for emergency research. This section will explain the processes used in this trial and the detailed rationale for compliance with the FDA regulations for EFIC found at 21 CFR 50.24.

5.1 Enrollments all performed under EFIC

All participants will be enrolled under EFIC. In this trial there will be no circumstance in which an informed consent process can be meaningfully or safely performed. All patients eligible for this trial must be unconscious from generalized SE, so no one can consent for themselves, and the rapidity with which treatment is needed for SE precludes obtaining consent from parents and other legally authorized representatives (LAR) even if they are present. Emergency treatment must be given quickly because every minute of delay decreases the likelihood that an anticonvulsant medication will be effective at terminating seizures, and patient morbidity and mortality increase with increasing seizure duration. Therefore, the delay related to any meaningful and compliant informed consent process is unsafe, impracticable, and would not be ethical. It is also not practicable to identify and consent patients prior to developing SE as 35-50% of patients who have SE are new onset, and even in patients with epilepsy, SE is a relatively uncommon and unpredictable manifestation. It is not possible to predict who will have SE.

A more detailed EFIC Plan document for the trial can be found in the Manual of Procedures (MoP). The investigational new drug application for this trial is identified as using EFIC. Investigators at each site will perform community consultation and public disclosure as discussed below, and these will be reviewed and approved by local institutional review boards prior to starting the trial at the site.

5.2 Consent to Continue Participation

Subjects or their LAR will be notified of enrollment as early as possible and consent to continue participation in the study will be sought for all subjects.

Attempts are typically initiated in the ED by the study team to discuss the enrollment with the subject in those subjects who are waking up, or to locate and communicate with an LAR for subjects who are not waking up. When a subject or LAR are first available to participate in an informed consent process, they will be asked to continue participation in the study. Continuation in the study only involves further review of the subject's medical record through the shorter of hospital discharge or 30 days. Those wishing to continue will have the informed consent document explained to them, will have any questions answered, and they will be asked to review and sign the informed consent document. In those who wish to discontinue participation, no further data will be collected. Data collected prior to withdrawal will remain in the study database as per FDA requirements and guidance. Those wishing to discontinue participation will also have the informed consent document explained to them, will have any questions answered and will be asked to review and sign an informed withdrawal from the study, however, subjects are not required to complete this document in order to withdraw. Standard consent procedures will be used. A copy of a model informed consent document will be provided to sites.

If a subject is randomized into ESETT and dies before a legally authorized representative or family member can be contacted, a reliable mailing address for the subject's family or LAR will be obtained. After allowing a two to four week period of grieving, the site study team will send a letter with basic information about the clinical investigation, the subject's inclusion, and contact information so that families can call or write to obtain more information or to get questions answered if desired.

5.3 Assessment of Notification and Consent Processes

Notification and informed consent logs are incorporated in the study case report forms and will allow tracking and reporting of the timeliness of these processes. In addition, subjects and LAR's participating in notification and consent processes may be offered an opportunity to share their experience and attitudes by answering a standardized survey up to day following an informed consent or withdrawal. This information will be used for process improvement and to better understand the subject or LAR perspective on emergency research.

5.4 Compliance with Criteria and Processes Required for EFIC

FDA regulations identify the specific circumstances in which EFIC is appropriate. ESETT fulfills these requirements for emergency research. In the following section, the components of the regulation are reproduced, along with an explanation of how ESETT will comply with each requirement.

SE is life-threatening and available treatments are unsatisfactory or unproven.

21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments

are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

Population studies of the incidence of SE report an incidence of between 41-61/100,000. The mortality rate is estimated to be greater than 17% (Neligan 2010).

The Cochrane review of anticonvulsant therapy for SE found eleven studies with 2017 subjects. The review concluded that lorazepam was the most effective agent and will terminate SE in only 60-70% of patients with this life-threatening condition. Because 30-40% of patients do not respond to first-line therapy for SE, benzodiazepines are unsatisfactory on their own. The three anticonvulsant medications studied in this trial are often used as second-line therapy to treat these patients but are unproven. There are no randomized, prospective, adequately controlled trials to confirm whether one or more of these medications are either effective or safe in these patients.

Clinical trials are clearly needed. No blinded, sufficiently powered prospective, randomized controlled trial has compared treatments for seizures refractory to initial benzodiazepine treatment. Currently published treatment guidelines recommend intravenous FOS as second-line treatment, with LEV and VPA as alternatives (Brophy 2012; Loddenkemper 2011; Meierkord 2010). However, there are small, open-label randomized studies that suggest the potential efficacy of VPA over LEV in treatment of ESE (Alvarez 2011). A series of clinical observations suggest that LEV and VPA are safe and effective in the treatment of ESE (Trinka 2009; Trinka 2011).

Obtaining prospective informed consent is not feasible.

21 CFR 50.24(a)(2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

Subjects in generalized status epilepticus are unconscious and unable to provide informed consent due to their medical condition. The care of patients in status epilepticus must be initiated immediately, which, in the Emergency Department care of patients with benzodiazepine refractory SE is the immediate initiation of second line anticonvulsant therapy.

Complications of prolonged seizures include impaired ventilation and subsequent pulmonary aspiration, cardiac dysrhythmias, derangements of metabolic and autonomic function, and direct injury to the nervous system. Seizures of short duration may be clinically benign, but longer durations are associated with increasingly severe morbidity and mortality. There is no specific identifiable threshold for seizure duration that predicts the onset of morbidity, and

thus, clinical practice is geared toward terminating seizures as quickly as possible.

Clinical data have demonstrated the duration of SE is associated with death and unfavorable neurologic outcomes (Maegaki 2005, Holtkamp 2005). While many of these data concern long durations of SE lasting hours or days, data also suggest that differences of as little as a few minutes in seizure duration are also associated with differences in outcome. Patients found in SE by paramedics who had termination of their seizures prior to arrival to the emergency department have an ICU admission rate of 32% as compared to 73% in patients whose seizures persisted on arrival to the ED. In a randomized trial, patients with SE treated with lorazepam or diazepam in the field by paramedics had mortality at hospital discharge of 7.7% and 4.5% respectively, which was less than half the mortality of 15.7% for patients in whom benzodiazepines were given only after arrival in the ED (Alldredge 2001).

The benefits of emergent treatment and termination of SE likely result from minimizing the consequences of impaired ventilation, pulmonary aspiration, hemodynamic instability, or metabolic derangements associated with prolonged convulsions. Rapid termination of seizures may also prevent kindling effects demonstrated in animal models in which seizures become more refractory to subsequent treatment as the duration of seizure increases (Morimoto 2004). Rapid treatment may also prevent the neuronal cell injury and loss that occurs with increasing duration of seizures due to duration dependent cytokine mediated effects (Ravizza 2005).

Since status epilepticus is precipitated by a variety of acute and unpredictable etiologies, there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research. Furthermore, status epilepticus is often an initial presenting manifestation of disease, precluding prospective identification. This was confirmed in data from Baren et al that found prospective identification of subjects for the PECARN Pediatric Seizure Study to be infeasible (Baren 2006).

Participation holds prospect of direct benefit to subjects

> *21 CFR 50.24(a)(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Participation in ESETT holds out the prospect of direct benefit to subjects. Subjects may directly benefit from participation because status epilepticus is a life-threatening condition and some of the interventions used in this study may be more effective than others. Studies in experimental SE in animals suggest that LEV may terminate established SE but that FOS, the

treatment most commonly used, fails to do so (Mazarati 1998; McDonough 2004; Prasad 2002). Some observational clinical data also suggests that FOS or its active metabolite PHT are not the most effective second-line agents (Agarwal 2007, Alvarez 2011). The use of response adaptive randomization in this trial increases the probability that those enrolled later in the trial will be more likely to be randomized to the more effective arm if there is a more effective arm.

The trial can not be practicably carried out without exception from informed consent

> *21 CFR 50.24(a)(4) The clinical investigation could not practicably be carried out without the waiver.*

This research could not be carried out without EFIC because treatment for SE needs to begin immediately upon ED arrival. Since SE patients are unable to consent for themselves and there is not time to obtain consent from an LAR, all patients must be enrolled under EFIC. A meaningful informed consent process requires that the LAR have time to understand the material presented, be able to ask questions and have time to think about what the patient would want. This is not possible in the brief period in which the study drug is obtained and initiated. In ESE, time to treatment is especially critical. Inability to obtain informed consent can limit the ability to discover better treatments for this critical and life-threatening condition.

Need for immediate treatment of status epilepticus precludes consent from an LAR

> *21 CFR 50.24 (a)(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.*

The narrow therapeutic window described above, the inability of patients with SE to communicate, and the inherent delay in delivery of standard therapy in attempts to contact and discuss consent with a surrogate decision maker preclude the possibility of obtaining informed consent for any potential subject in ESETT. Attempts to contact LAR for notification and consent to continue participation will be tracked and can be summarized and reported to the IRB at the initial and continuing reviews.

Provision of an informed consent document

> *21 CFR 50.24(a)(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.*

A written informed consent document prepared at each site for this study must be reviewed and approved by participating IRB's approving this clinical investigation. Subjects enrolled in ESETT, or their legally authorized representatives (LAR) or family, are informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity. The study team is immediately notified of the arrival of treated subjects in the emergency department (ED). An on call study team member quickly responds to the ED to complete the subject enrollment. The subject (or LAR or family) is approached, and an informed consent process initiated as soon as possible. The study team notifies the subject or LAR/family about the subject's enrollment, provides information about the study and about the subject's rights and the responsibilities of the investigators, and answers any questions about the study and further participation. A written informed consent document is used to reinforce the information provided verbally and to document a decision to either continue in the study or to not participate any further. A copy of this form is provided to the subject and another copy is placed in the research record.

Community Consultation

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn*

The community will be consulted prior to the initiation of research. With guidance from the each site's IRB, the community will be asked to give their opinions of the research. A menu of options is included in the detailed EFIC plan in the MoP and includes mechanisms such as community meetings, town hall meetings, focus groups, meetings with established community advisory boards, in-person surveys, and random-digit dialing surveys. The specific type of community consultation will be determined by each site's IRB. Reporting of community consultation results will be standardized across the ESETT sites.

Public Disclosure

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results*

Public disclosure is the primary element in making certain that ESETT is conducted in an entirely transparent manner. Methods of announcing information about the trial, and the development of advertising and other materials about the trial, will take place both locally and nationally. Public disclosure will be initiated prior to approval of the trial, may continue during enrollment, and will conclude with dissemination of study results after the trial is completed. A menu and

discussion of many public disclosure methods and procedures is detailed in the EFIC plan in the MoP. Each site IRB will determine the type and form of local public disclosure. Reporting of public disclosure efforts will be standardized. Summaries of public disclosure will be reported to each IRB, and composite reports of local and national public disclosure at the trial-level will be provided to the FDA docket.

Data Monitoring Committee

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;*

A Data and Safety Monitoring Board (DSMB) is appointed by the NINDS to provide ongoing evaluation of safety data as well as the overall conduct of the trial, per institute guidelines. The members will have a meeting with the study team prior to study commencement to discuss the protocol as well as content and format of the DSMB reports. The SDMC will prepare requested reports at specified time intervals. Data and safety monitoring will be performed consistent with the guidance provided by the NIH notices 98-084 “Policy for data and safety monitoring” and OD-00-038 “Further guidance on data and safety monitoring for phase I and phase II trials”, and by the NINDS document based on these notices “NINDS Guidelines for Data and Safety Monitoring in Clinical Trials”.

Contacting Other Family

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: …. (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

It will not be ethically possible in ESETT, for the reasons described above, to delay treatment of the seizing subject long enough to contact either an LAR or other family members. A provision of the protocol has been made to allow subjects that learn of the trial through public disclosure efforts or other means, and who would not want to participate if treated in the ED for status epilepticus, to communicate that decision to the ED without causing any delay in treatment. As part of the primary assessment of a seizing patient, ED providers already check for medical alert jewelry to ascertain emergent medical information about the patient. If the words “ESETT declined,” or alternative designation as defined in the MoP, are listed on the medical alert tag, the patient will not be enrolled in the clinical investigation. Medical alert tags are commonly used by people with epilepsy already, and provide a means of communication that does not require such patients to wear any extra marker. Since they are already worn daily, they do not require additional effort to use once information is added to the tag. The tags are common and

effective for communicating information to medics while still being inconspicuous. Use of this enrollment exclusion will be tracked and this information made available to IRBs at the time of continuing review.

Post Enrollment Notification and Consent to Continue

> *21 CFR 50.24(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.*

Subjects enrolled in ESETT, or their legally authorized representatives (LAR) or family, are informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity as detailed above and in the MoP. It is anticipated that the notification of subjects, or their families or LAR, will most commonly take place in the ED within hours of subject enrollment. Attempts to notify the subject or an LAR are repeated until successful. All notification attempts are logged and recorded in the subjects online case report form in WebDCU™. Reports of these logs will be available for inclusion in annual reports to the respective IRBs.

Record Keeping

> *21 CFR 50.24(c) Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA.*

Records documenting the enrollment of patients using EFIC, procedures for notification of enrollment, and informed consent forms will be kept for a minimum of three years after completion of the clinical investigation.

IND Requirement

> *21 CFR 50.24(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as*

amendments under Secs. 312.30 or 812.35 of this chapter.

This trial requires an IND, review and approval by the FDA. No enrollment can commence unless approval by the FDA and participating IRBs is obtained. The Study Principal Investigator serves as the sponsor of the IND. Discussions with the FDA have clarified that a single IND is appropriate for the proposed trial.

Communication of IRB Determinations

> *21 CFR 50.24(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.*

If an application for ESETT is disapproved by a local IRB at any site, the Hub principal investigator will inform the ESETT principal investigator and IND sponsor and provide him with the written findings of that IRB. The Study PI/sponsor will promptly disclose this information to the FDA, and to all participating Hub PIs who will be instructed to submit these to all IRBs to which applications for ESETT have been submitted for review. If there is a change in the study protocol, then there must be a re-review of the protocol by all the IRBs of the participating institutions.

6. STUDY ENROLLMENT PROCEDURE

6.1 Screening

The goal is to include all eligible patients who present to participating EDs. All patients presenting with a diagnosis of seizures or convulsions will be evaluated for participation in the study. A screen failure log will include patients with a diagnosis of seizures or status epilepticus who are not randomized into ESETT.

6.2 Enrollment

Study processes will not delay clinical treatment. When an eligible patient presents to the emergency department, the clinical team will access the age appropriate ESETT "use next" box. To ensure treatment is not delayed, the "use next" box must be easily accessible and maintained in proximity to patient care in the ED. Most often, this will be in the secured ED medication dispensing system or the ED pharmacy.

The clinical team opens the "use next" box. The protocol assist device is activated. The weight based infusion rate is determined from the dose administration chart. If the patient is a child, the length based weight estimation tool is used to determine dose unless an accurate weight is known. An infusion pump is programmed with the determined rate and the infusion line is primed. The infusion is then started and the timer is started on the protocol assist device.

The study team should be alerted at this time, if not already done.

Study drug is administered by pump for ten minutes (except as noted in section 7.3). The infusion is then discontinued and discarded. The patient should then be observed for 10 more minutes, until 20 minutes after the start of study drug infusion. Rescue therapy is not indicated during this period. After 10 minutes from the end of study drug infusion, rescue therapy should be given as deemed clinically indicated by the care team for persistent or recurrent seizures.

The primary outcome is determined at 60 minutes.

6.3 Study Team Arrival

The study team should be activated as early as possible without delaying treatment. The care team follows the protocol but does not engage in research. Questions about eligibility are determined by the study team. The study team will arrive in the ED as soon as possible.

Upon arrival, the study team will assist the clinical team in completing the protocol. After arrival the study team will seek an LAR to notify of the subject's participation and to determine consent to continue. The study team maintains a log of attempts to locate an LAR, of notifications, and of consent decisions.

The study team will collect and complete the ED-enrollment case report form, will collect the spent “use next” box and protocol assist device, and will process, reload, and place a new “use next” box.

6.4 Blood Draw

Up to 2 tubes of blood, approximately 5 mL total (2.5 mL each), may be drawn from a subset of subjects after the study drug infusion to confirm drug levels and accurate assignment as needed to ensure study performance.

6.5 Enrollment Flow Diagram

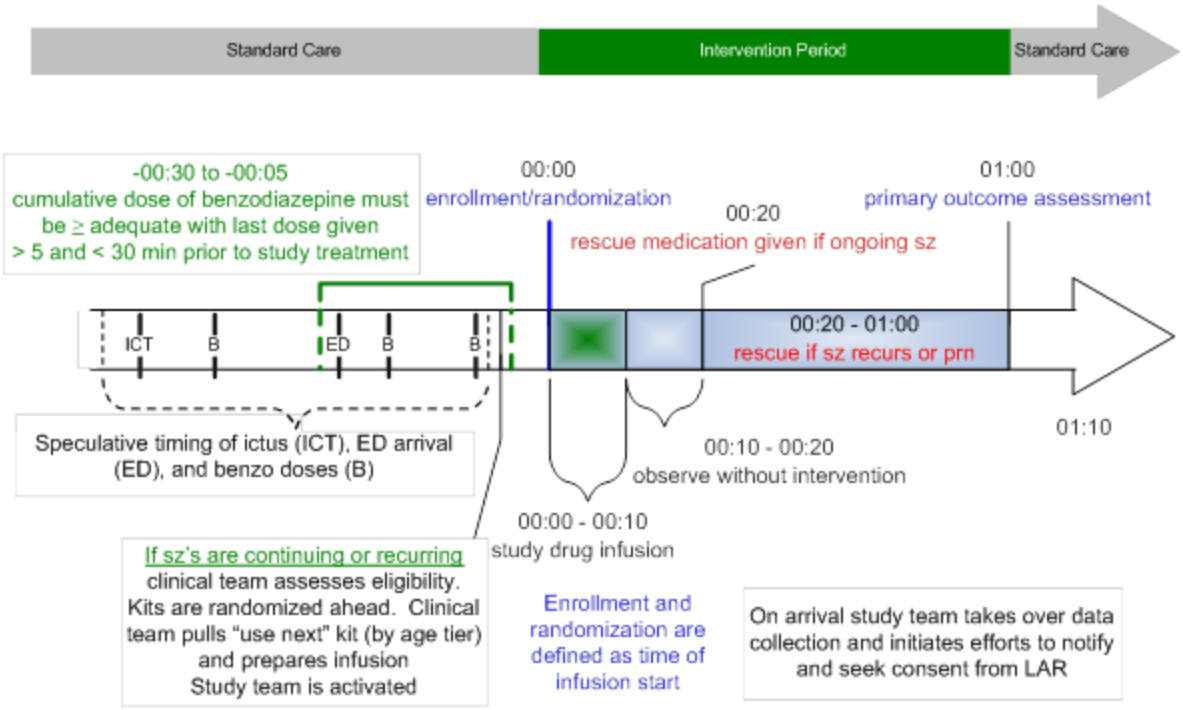

Figure 7.

7. STUDY INTERVENTIONS

7.1 Determination of subject weight

The rate of study drug infusion is based on estimated patient weight. The subject's weight may be obtained from reliable caregivers or records. In children, if an accurate weight is not known, dose will be determined using the length-based weight/dose estimation tool included in the "use next" box, (akin to the Broselow tape). In adults and the elderly, weight will be estimated in the manner as in standard care for weight-based dosing of other resuscitation/critical care drugs. A measured weight may also be used if available, but it is expected that the clinical scenario will usually preclude weighing the subject.

7.2 Study drug administration

Study drugs will be administered intravenously. For purposes of this study, intraosseous (IO) access will always be considered equivalent to IV access. Infusion pumps will be used to ensure that study drug is administered over 10 minutes.

The infusion pump will be programmed to deliver the volume/rate indicated on the dose administration chart (table 3). The volume and rate will be confirmed by a second nurse. Infusion will last 10 minutes. Priming the line prior to infusion and removing the line at the end of infusion are performed in a manner that ensures the entire study volume of study drug is delivered in accordance with local nursing practice.

Table 3. Dose Administration Chart

Subject Wt (kg)	Infusion Vol. (mL)	Infusion Rate (mL/min) over 10 min	FOS dose (mg PE)	LEV dose (mg)	VPA dose (mg)
7.5 to <10	9	0.9	150	450	300
10 to <12.5	12	1.2	200	600	400
12.5 to <15	15	1.5	250	750	500
15 to <20	18	1.8	300	900	600
20 to <25	24	2.4	400	1200	800
25 to <30	30	3	500	1500	1000
30 to <35	36	3.6	600	1800	1200
35 to <40	42	4.2	700	2100	1400
40 to <50	48	4.8	800	2400	1600
50 to <60	60	6	1000	3000	2000
60 to <70	72	7.2	1200	3600	2400
70 to <75	84	8.4	1400	4200	2800
≥75	90	9	1500	4500	3000

7.3 Study Drug Infusion Precautions

Study drug infusion precautions are the same as in standard care in patients with status epilepticus. Heart rate and rhythm, blood pressure, and oxygen saturation are monitored.

If hypotension or cardiac arrhythmia occur during study drug infusion, the infusion rate will be reduced by 50% (increasing the infusion time and maintaining the planned volume).

In this context, hypotension is defined as sustained systolic blood pressure <90 mm Hg in subjects 13 years and older, <80 mm Hg for 7 years to <13 years, and <70 mm Hg for 2 years to <7 years. Intravenous fluid may also be used for initial treatment of hypotension.

If hypotension or cardiac arrhythmia persist, or as determined appropriate by the care team, the drug infusion will be discontinued. Persistent hypotension or arrhythmia will be treated

according to local standard care after the study drug is stopped.

Treatment with study drug may also be terminated for any serious adverse event during infusion that the treating physician believes is study drug related.

Discontinuation of study drug does not affect participation of the subject in the study. All subjects should be followed until they reach their end of study.

7.4 Randomization

Due to the emergency nature of ESE, randomization must not delay treatment. To complete the randomization quickly, the study drug will be preassigned using a central randomization process via WebDCU. The mortality associated with SE and etiology of SE varies with age. In addition, certain adverse effects of drugs such as hypotension are more common in the elderly compared to the pediatric age group. For these reasons, randomization assignments will be stratified by age group (less than 18 years, 18-65 years, and greater than 65 years).

Prior to enrollment at each site, the randomization assignment is made [for each of the three age strata]. The assigned study drug is installed in the "use next" box. When the next eligible subject at the clinical site is identified, the ED nurse or physician, selects the "use next" box [for that stratum].

Once the infusion pump, connected to study drug vial and patient's IV catheter, is turned on, the patient is considered to have been randomized into the study. After a patient is randomized and the study team member enters the randomization form into WebDCU, the next treatment assignment is made, and a new "use next" box can be prepared. Hence, after each subject is randomized, the treatment assignment is made for the subsequent subject (within that stratum) once the current subject's randomization data are entered into WebDCU.

Sites may also be contacted and asked to go to WebDCU to reassign the content of the "use next" box when randomization in the trial is updated.

7.5 Study Drug

Study drug will be produced at the central pharmacy, a GMP facility at University of California, Davis. Diluted formulations are expected to remain stable for months when stored at 2-8 °C. Expiration dates for study drug will be determined and adjusted based upon ongoing stability testing performed on study drugs prepared at the GMP facility for the study.

All three formulations will be pale yellow solutions. None are reported to consistently cause infusion-site adverse effects. The method of drug administration, including volume and rate of infusion is identical for all three drugs. These factors ensure that drug administration will be

blinded.

The drugs will be formulated in the following concentrations: FOS 16.66 mg PE/ml, VPA 33.33 mg/ml and LEV 50 mg/ml. The dose will be FOS 20 mg PE/kg, VPA 40 mg/kg, and LEV 60 mg/kg, increasing up to a weight of 75 kg. At this weight the maximum safe dose for a 10 minute infusion period for adults is reached. A 10 kg patient would receive drug infusion at the rate of 1.2 ml/min and those weighing 75 kg or more will receive drugs at an infusion rate of 9 ml/min.

7.6 Study Drug Packaging

Study drug will be prepared in 100 mL glass vials, labeled as investigational, and coded with unique human readable ID numbers and barcodes. Because this is a blinded study, nobody at the site (local pharmacy, clinical team, and study team) will know whether the next assignment is FOS, VPA, or LEV.

"Use next" boxes will be prepared at the site and contain: 1) a 100 ml glass vial containing either FOS, VPA, or LEV, 2) a dose administration chart, 3) a protocol assist device, and 4) a length based weight/dose estimation tape (similar to Broselow tape).

7.7 Protocol Assist Device

The protocol assist device is a mobile electronic platform, such as the Apple iPod Touch, with an ESETT app loaded on it. It is intended to assist the clinical and study team in performing the study protocol. The app will be started by the treating physician or nurse and will guide the team through the initial phase of the study. The device is intended to serve several functions including: confirmation of correct randomization code, time keeping during infusion and evaluation, supplemental data logging, and support of rapid emergency unblinding.

The protocol assist device should be kept at subject's bedside until retrieved by the study team.

8. OUTCOME ASSESSMENT AND POST-INTERVENTION

8.1 Assessment of treatment effect

Assessment of treatment effect is performed at 20 minutes and 60 minutes after the start of study drug infusion.

"Start of study drug infusion" is considered the time of randomization. It is the time when the study drug infusion is begun by starting the IV infusion pump.

Absence of clinically apparent seizure at 20 and 60 minutes is determined clinically. Clinically apparent seizure is defined as obvious focal or generalized tonic clonic movements, nystagmoid or rhythmic eye movements, or generalized or segmental myoclonus at the time of assessment.

Patient's responsiveness to verbal command or noxious stimuli is observed at 20 and 60 minutes. Responsiveness at time of assessment is always compared to that at the time of randomization. Generally, improvements in responsiveness are characterized by purposeful responses to noxious stimuli, the ability to follow commands, or verbalization. The Richmond Agitation Scale Score will be recorded and may be used to assist in this determination.

8.2 Determination of primary outcome

The primary outcome will be determined 60 minutes after the start of study drug infusion. The primary outcome may be determined by the study team if present, or by a treating ED physician on the clinical team if the study team is not yet available. The primary outcome is based upon the assessment of treatment effect at 60 minutes as defined above, and the use of additional anti-seizure medications. Ongoing seizures at the time of determination of the primary outcome, whether persistently or recurringly, indicates a failure to meet the primary outcome. Transient seizure recurrence followed by cessation, however, is consistent with meeting the primary outcome.

Medications qualifying as "anti-seizure medications" for the purpose of determining the primary outcome are detailed in the study Manual of Procedures. The administration of the these anticonvulsant or sedative medications for recurrent seizures or any other reason, by any route, within 60 minutes after the start of study drug infusion indicates a failure to meet the primary outcome.

The primary outcome should be based on the assessment of what the treatment effect and the condition of the patient were at 60 minutes after the start of study drug infusion based upon all information available to the assessor at the time the primary outcome is documented.

Death prior to 60 minutes after the start of study drug infusion indicates a failure to meet the primary outcome.

The primary outcome may be documented in more than one location. The highest level of source document in the established hierarchy will be considered the primary source document for the primary outcome. The hierarchy of source documents that will be used to confirm the primary outcome outcome is:

1. Contemporaneous observation and documentation. The primary outcome is observed by the study team at the bedside and directly recorded on the CRF or on the study book worksheet. Direct data entry in WebDCU is preferred but not required.
2. Direct communication with the clinical team. The study obtains the primary outcome data by direct explicit communication with the treating ED attending physician. Communication should occur and be documented as close to the time of assessment as possible.
3. Protocol Assist Device. The primary outcome explicitly recorded on the protocol assist device will be treated as a source document and may be used to complete the CRF if contemporaneous recording or direct communication with the study team are not available.
4. Medical Record - explicit study specific documentation. If the medical record is used as a source document, the adjudicators will determine the primary outcome from an explicit study specific template note if available in precedence among available documentation.
5. Medical Record - implicit review. If the medical record is used as a source document, and no explicit study specific template note is available, the adjudicators will determine the primary outcome from their interpretation of provided documentation.

8.3 Determination of secondary outcomes

The primary safety outcome is the absence of life threatening hypotension and cardiac arrhythmia within 60 minutes of the start of study drug infusion.

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.

Life-threatening cardiac arrhythmia is defined as any arrhythmia that persists despite reducing rate of study drug infusion, and that requires termination with chest compressions, pacing, defibrillation, or use of an antiarrhythmic agent or procedure.

Additional predefined safety outcomes include mortality, need for endotracheal intubation

within 60 minutes of start of study drug infusion, acute seizure recurrence within 12 hours, and acute anaphylaxis.

Mortality is determined by survival to subject end-of-study (hospital discharge or 30 days, whichever comes first). All causes of mortality are included.

Need for endotracheal intubation within 60 minutes of start of study drug infusion includes any placement or attempt at placement of a definitive tracheal airway (orotracheal, nasotracheal, cricothyroidotomy, or tracheostomy) for support of respirations or protection of airway. The use of non-definitive and/or non-tracheal airways (oral or nasal airways, laryngeal mask airways, or esophageal obturator airways) is not included if the patient is not subsequently intubated unless specifically deemed to have been used in lieu of tracheal intubation.

The RASS may be determined by the care team or the study team. The RASS scoring system is fully described in the manual of procedures.

Acute recurrent seizure is defined as definitive convulsive or electroencephalographic seizure activity triggering further anticonvulsant therapy occurring between 60 minutes and 12 hours after the start of study drug infusion. This definition does not include those given further anticonvulsants as secondary prophylaxis or as treatment for vague or uncertain exam findings or nondiagnostic electroencephalography.

Acute anaphylaxis is defined as a clinical presentation consistent with life threatening allergic reaction occurring within 6 hours of the start of study drug infusions and manifested as urticaria in combination with either (1) a systolic blood pressure of < 90 mmHg sustained for greater than 5 minutes, or (2) objective evidence of airway obstruction, and for which the patient was treated with antihistamines and/or steroids.

Respiratory depression is defined as impairment of ventilation or oxygenation necessitating definitive endotracheal intubation and mechanical ventilation. It is distinct from intubations performed only for airway protection in those with decreased levels of consciousness. It does not include those getting only supraglottic airways or transient bag-valve-mask support.

Secondary efficacy outcomes include time to termination of seizures, admission to ICU, and the length of ICU and hospital stays.

The time to termination of seizures is the interval from the start of infusion of study drug to cessation of clinically apparent seizure in those who meet the primary outcome.

Hospital and ICU admission from the ED, and length of stay, is abstracted from the hospital admission record. ICU admission is recorded as occurring only if the ICU is the initial inpatient unit for the patient. Length of stay is determined by the number of calendar days after the day

of ED arrival until hospital discharge or subject end-of-study.

8.4 Endotracheal intubation

Elective or semi-elective endotracheal intubation (e.g. for imaging studies, etc.) should be delayed until after determination of primary outcome if possible. Emergency endotracheal intubation should not be delayed. The need for emergency intubation is determined by the care team. It is generally not necessary to perform emergency endotracheal intubation for prolonged unresponsiveness alone in this patient population. Emergent or elective endotracheal intubation and its indication should be carefully documented, including all medications administered.

8.5 Rescue anticonvulsants

Subjects who do not respond to the study drug and continue to seize >20 minutes after the start of study drug infusion (>10 minutes after the completion of study drug infusion) will need additional anticonvulsant therapy for SE at the discretion of the treating team. The treating physician will follow local practice guidelines in choice of a third line agent for the treatment of SE. Appropriate third line choices include phenobarbital or a general anesthetic such as propofol, midazolam or pentobarbital when a second-line agent has failed. Finally, some centers may choose to use another second line agent. If the care team feels that another second line agent is indicated and that knowledge of the study drug given is needed to guide this selection, emergency unblinding should proceed as described below in section 10.2.

8.6 Continuous EEG

Continuous EEG should be performed as indicated by the care team consistent with standard clinical practice. If indicated, cEEG should be initiated as early as possible.

8.7 Standard supportive care

Other than as indicated in this protocol, subjects will receive the usual care and evaluation provided at each site. Sites may wish to reference the practice parameter recommendations for status epilepticus of the American Academy of Neurology (Riviello 2006).

9. ADVERSE EVENTS

9.1 Definitions of Adverse Events:

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

A Serious Adverse Event (SAE) is any adverse event that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, or requires intervention to prevent permanent impairment or damage. For the purposes of this study, we specifically exclude hospitalization for the sole purpose of observing a patient after SE as a Serious Adverse Event.

9.2 Grading of Adverse Events

All adverse events (AEs) occurring within 24 hours of treatment and all serious adverse events occurring during study participation will be documented on the AE case report form. The severity of adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (Version 4.03, June 2010, CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v 4.03) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Table 4.

Grades	Descriptions of severity for each AE based on this general guideline
Grade 1 Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 Moderate	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3 Severe	medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4 Life-threatening	urgent intervention indicated
Grade 5 Fatal	Death related to AE

Severity is not equivalent to seriousness. A serious adverse event (SAE) would be any event in

category 4 or 5, and any event in category 3 that required or prolonged hospitalization. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade Selection i.e., Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

9.3 Relationship to Study Treatment

One of the most important components of AE reporting is determining the cause of the AE. It is imperative that the investigator assess AE causality in terms of overall study participation and make an independent determination as to whether the AE was thought to be related to any study-related activity (i.e., study intervention,). Determination may be particularly challenging in ESETT since typical criteria for assessing causality such as evaluation of the effects of de-challenge and re-challenge are not possible within the scope of this protocol in which study interventions are isolated single exposures of short acting medications. In addition the underlying cause of SE: stroke, infection, inflammation etc. cause adverse events. Finally, prolonged seizures of SE cause adverse events. For each adverse event, the relationship to the study treatment must be recorded as definitely, probably, possibly, unlikely, not related. The NETT modified "Algorithm to Determine Relationship of Adverse Event to Study Agent" will be used for all relatedness determinations in ESETT, and is found in the Manual of Procedures.

9.4 Adverse Event Reporting

All AEs occurring within 24 hours of study treatment and all serious adverse events (SAEs) occurring until participation in study has ended (discharge from the hospital, death, or 30 days since enrollment) are recorded on the online AE case report form (CRF) through the WebDCU™. The site PI or Study Coordinator or designee is responsible for entering all AEs and SAEs and updating the information (e.g., date of resolution, action taken) in a timely manner. All non-serious AEs must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. For SAEs, the data entry must take place within 24 hours of discovery of the event.

The site PI is responsible for the monitoring and follow-up of AEs until resolution (or end of study for that subject) and appropriate documentation in the subject research record. In addition to performing protocol-specified follow up, the participating PI must review all previously reported ongoing AEs to evaluate the current status. If an AE that was previously reported on the Adverse Event CRF fully resolves and then recurs at a later date, the second occurrence is considered a new AE and a new Adverse Event CRF must be completed. Likewise, if an SAE that was previously reported and subsequently fully resolved later recurs at a level requiring expedited reporting, the SAE must be reported as a new SAE on the Adverse Event CRF.

9.5 Expected Adverse Events

Expected adverse events include side effects known to be potentially associated with the study medications as listed in the study drug package inserts, and complications that commonly occur as a result of the underlying condition or as a result of hospital care. The outcomes and events defined below are likely and anticipated and will be closely tracked.

These include the secondary safety outcomes previously defined in section 8.3:

- Life-threatening hypotension
- Life-threatening cardiac arrhythmia
- Mortality
- Need for endotracheal intubation
- Acute recurrent seizure
- Acute anaphylaxis
- Respiratory depression or failure resulting in intubation.

Other defined expected adverse events include:

Hepatic transaminase or ammonia elevations, defined as those levels determined by the site investigator to be greater than 3 times the upper limit of normal or otherwise clinically significant.

Purple glove syndrome, defined as the presence of all three of the findings of objective edema, discoloration, and pain in the distal extremity in which study drug was administered, with or without known extravasation, and for which there is no other evident etiology.

9.6 Clinical Management of Adverse Events

All adverse events will be managed according to local institution guidelines and treating physician's judgment. Specific recommendations for managing acute adverse events during drug infusion are included above in Section 7.3.

10. STATISTICAL CONSIDERATIONS

10.1 Randomization

The randomization scheme will be equal allocation (1:1:1) for the first 300 patients. Once 300 subjects are enrolled, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm (Connor 2013). The target allocation ratio will be updated every 100 patients. We will use a "Step Forward" centralized randomization procedure developed for emergency treatment trials. (Zhao 2010) Randomization will be stratified by age.

10.2 Blinding and unblinding:

Patients and emergency department study team members are blinded to the treatment assignment, as are the PIs and clinical coordinating center (CCC). Blinding is provided by the use of the same color of formulations, same drug packaging, and same method of drug administration in every subject.

Emergency unblinding may be required if the treating team feels that subjects' care after the study intervention requires knowledge of what study drug was given. Emergency unblinding will not be performed within 60 minutes of the start of study drug infusion. The blind should be maintained until after the primary outcome has been collected.

Emergency unblinding performed prior to 60 minutes or prior to determination of the primary outcome, because of physician judgment that it is necessary for the safety or care of the patient, or because of unanticipated situations is accommodated by calling the hotline but is a deviation from this protocol.

10.3 Primary outcome

A patient is considered a treatment success if they meet the definition of the primary outcome as defined above.

10.4 Secondary outcomes

Secondary outcomes are intended to show safety, congruence or divergence from the primary outcome, or to provide additional detail that helps to more fully describe or interpret the effects of the treatment, the study population, or the clinical scenario.

10.5 Primary Analysis

The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods. This trial will be considered a success if the probability that a treatment is the most effective is greater than 0.975 or the probability that a treatment is the

least effective is greater than 0.975 for any treatment.

Each of the three treatment arms is modeled independently. We assume the probability of response has a uniform Beta(1,1) prior distribution. We assume the number of responses on each treatment arm follows a binomial distribution. We update the prior distribution with the observed data and use the resulting posterior distribution to calculate the probability that each treatment is the most effective and the probability that each treatment is the least effective. The posterior distribution for each treatment arm will therefore be Beta(1+ # of Successes, 1+ # of Failures).

At the conclusion of the trial, we will report the response rates for each treatment group with 95% credible intervals and the pairwise differences in responses rates and corresponding 95% credible intervals of those differences.

10.6 Frequentist Analysis of the Primary Outcome

At the final analysis, the global null hypothesis that the probabilities of success for all three treatment groups are equal will be tested in a chi-squared test with 2 degrees of freedom. If, and only if, the three-way, global null hypothesis is rejected, then all pairwise comparisons will be performed as a two-sample test of difference in proportions (Z - test). Although the Frequentist tests will only occur once, we will use Pocock boundaries to control the overall alpha.

10.7 Interim Analyses

Interim monitoring for success and futility will begin after 400 subjects have been randomized and will be repeated after every additional 100 subjects are randomized. This trial will stop early for success if we have identified the maximum effective treatment with a least 97.5% probability.

There are two early futility criteria. The first futility rule will stop the trial early if all treatment arms have a clinically unacceptable response rate. The second futility rule will stop the trial early if all treatments are performing similarly and we will be unable to identify a most effective or least effective treatment.

Following review of both the interim analysis results and safety data, the DSMB will make a recommendation regarding the above stopping rules.

10.8 Estimated accrual

Estimates of accrual for purposes of statistical planning assume 40 enrollment sites averaging 5 subjects per year over a 4 year enrollment period.

10.9 Sample size considerations

This study will enroll a maximum total sample size of approximately 795 patients over 4 years, at an accrual rate of approximately 16.5 patients per month. A sample size of 795 provides approximately 90% power to identify the most effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (an absolute difference of 15%). The trial operating characteristics were determined via an extensive simulation study. The statistical and full simulation details as well as the operating characteristics of the design have been published (Connor 2013).

The expected response rates for FOS, LEV and VPA are based on the retrospective analysis of 279 episodes of established SE in adults, who were treated with PHT, LEV or VPA (Alvarez 2011). The study reported 59.6% of patient episodes responded to PHT, 51.7% to LEV and 74.6% to VPA. Based on this study and expert evaluation of all currently published data on the treatment of established SE, we expect that the worst drug will be effective in 50% of the patients. A 15% difference is the minimum clinically important difference sufficient to change clinical practice.

The total sample size for this trial corresponds to the sample size that would be needed for a frequentist analysis. A sample size of 209/group (627 total) is needed for a chi-squared test with 2 degrees of freedom of the overall test of equality of the three proportions with 90% power (assuming the smallest proportion is 0.50 and the largest proportion is 0.65 and the average proportion is 0.55, two-sided alpha 0.05). For a two-sample test of proportions (all pairwise comparisons of treatment groups), with equal allocation into each treatment group, when one treatment proportion is 0.50 and the other treatment proportion is 0.65, the sample size needed is 240 per group to detect an absolute treatment difference as small as 0.15 with 90% power (assuming two-sided alpha 0.05 and interim looks). Thus, a total sample size of 240*3 groups=720 (uninflated for re-enrollers, missing data). Given the possibility of re-enrollers, protocol violations, and missing data, the maximum sample size was inflated from 720 up to 795 by N`=720*R where R=(1/(1-.025)^2)*1.05. The sample size was inflated in two ways. First, for the re-enrollers (expected to be 5%) who will be excluded from the analysis. Secondly, to account for the impact of treatment cross-overs, protocol violations, and missing data on the ITT analysis (expected to occur 2.5% of the time). In order to determine the operating characteristics for this Bayesian adaptive design, simulations were performed assuming a maximum sample size of 720 (the uninflated maximum) and considering different response rate scenarios.

10.10 Missing Data and Non-compliance

The primary analysis will be analyzed under the intent-to-treat principle (ITT). The ITT evaluable sample will include all subjects who are randomized. Subjects that are enrolled more

than once during the study period will have only their first enrollment included in the primary analysis. It is anticipated that a maximum of 5% of subjects will be re-enrolled. In an ITT analysis, missing data and treatment cross-overs can be problematic. Due to the short term endpoint, minimal missing data is expected for the primary outcome. However the inability to administer the full dose of the study drug, or other protocol violations may occur and attenuate the treatment effect. It is anticipated that a maximum of 2.5% of data will be missing or involve treatment cross-overs. Any missing values will be considered a treatment failure.

10.11 Secondary Analyses

Secondary analyses of primary outcome will include an analysis of the adjudicated primary outcome, a re-enroller analysis, a per protocol analysis, an analysis by age. Exploratory analyses of the primary outcome will assess treatment differences adjusting for etiology, time from seizure onset to randomization, and enrolling site. Clinically important differences in the treatment effect due to sex/gender, racial, or ethnic differences are not expected, but will be explored. Secondary and exploratory analyses will not be adjusted for multiple comparisons.

10.12 Analysis of Secondary Outcomes

The secondary outcomes will be compared by treatment group. All secondary outcomes will be tested at a significance level of two-sided alpha of 0.05. Binary outcomes will be compared by first testing the null hypothesis that the proportion of responses for all three treatment groups are equal in a chi-squared test. If the three-way null hypothesis is rejected, then all pairwise comparisons will be performed as two-sample tests of proportions. Continuous outcomes will be compared in an F-test to test the null hypothesis that all three treatment groups are equal, followed by pairwise t-tests. Kaplan Meier curves and log rank tests will be used to compare time to event outcomes by treatment group.

10.13 Pediatric Subgroup Analysis

The interaction of age group and treatment group will be tested at each interim analysis. If there is sufficient evidence of an interaction, then the response-adaptive randomization will be stopped and randomization will revert to equal allocation until the end of the trial.

Regardless of whether an interaction between age group and treatment is detected, the primary analysis will be redone by age group (children age 2-18, adult 19-65, and Seniors, >65).

11. DATA COLLECTION

11.1 Study activity and data collection

Follow up data collection: Very limited clinical data will be collected during hospitalization, beyond that available and collected in the ED. Hospitalized subjects should be reevaluated the day after admission for adverse events. At the end of hospitalization, subjects should again be evaluated for serious adverse events. Seizure etiology and hospital/ICU length of stay are also determined at discharge.

11.2 Data Collection Schedule

Data elements will be detailed in the CRF study book which is available for download under Project Documents on WebDCU™

Table 8. Schedule of Assessments

	Day 1 (data collected in the ED on the day of enrollment)	Day 2 (24-48 hours after study drug infusion)	End of Study*
Eligibility	X		
Randomization	X		
Primary outcome	X		
Safety outcome: hypotension; cardiac arrhythmia	X		
Richmond Agitation and Sedation score (RASS)	X		
Demographics	X		
Post enrollment consent to continue	X**		
Probable cause of status epilepticus			X
Adverse Events	X	X#	X
Endotracheal Intubation	X	X#	
EEG			X
Time to termination of seizures	X		
Admission to ICU			X
ICU length of stay			X
Hospital length of stay			X
Study Drug infusion log	X		
Prior/Concomitant meds	X		
Vital Signs	X		
End of Study			X

* Hospital Discharge or 30 days from enrollment whichever comes first

** Or earliest opportunity if not possible in the ED

Optional repeated forms

11.3 Quality assurance

The study will be conducted in accordance with the ICH Guidelines for Good Clinical Practice and all relevant local, national and international regulations.

Please refer to the NETT monitoring standard operating procedures (SOP) at http://nett.umich.edu . In brief summary, Hub investigators will provide quality assurance within their Hub spoke complex in a process that, in this network, will be called Verification. This is independent of Monitoring, which, in this network, is used to mean only independent external monitoring by the NETT Project Monitor of the Clinical Coordinating Center (CCC).

Data quality monitoring is performed continuously. Out of range and logical errors are identified at the time of data entry.

Site visits will be conducted periodically by the Project Monitor(s). Details of the content of site visits are found in the monitoring plan in the MoP. In brief, the primary purpose of the site visit is to confirm that local regulatory documents are being properly maintained, and to compare data reported on case report forms with source documents, including documentation of informed consent and proper reporting of adverse events.

Some combination of risk based allocation of site and remote source document verification will be used over the course of the trial.

11.4 Data management

The NETT Statistical and Data Management Center (SDMC) will provide data management for the ESETT study. The SDMC is housed in the Data Coordination Unit (DCU) at the Medical University of South Carolina (MUSC). Data entry will occur at the enrolling sites using a web-based data entry system, WebDCU™. A central reader form will be entered into WebDCU at the NETT CCC at the University of Michigan.

11.5 Clinical adjudication Core

The clinical adjudication core will determine key clinical characteristics for each patient enrolled including the etiology of status epilepticus and the duration of seizures prior to enrollment.

The primary outcome is based on site determination, but the adjudication core will review all primary outcomes for consistency and will determine the reasons for failure of therapy in those patients who do not meet the primary outcome. Packets of de-identified medical records will be available to the adjudicators as needed. The adjudicators will be blinded to treatment assignment.

12. HUMAN SUBJECTS

The protection of human subjects is of primary importance in clinical research and in this clinical trial. Clinical treatment teams must assess and treat patients with SE rapidly. This trial has been designed to avoid delays of treatment of even just a few minutes because longer delays may increase morbidity or mortality. See section 5 of this protocol for an extensive discussion of the use of EFIC and related processes in this trial.

12.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (see template) and any subsequent modifications will be reviewed and approved by the IRB for each site responsible for oversight of the study.

12.2 Data and safety monitoring board (DSMB)

A Data and Safety Monitoring Board (DSMB) appointed by the NINDS will provide ongoing evaluation of safety data as well as the overall conduct of the trial. The DSMB will be formed by the NINDS as per institute guidelines. The SDMC statisticians will generate Data and Safety Monitoring (DSMB) Reports semi-annually or more frequently as needed. This review will aid in identifying any safety issues that may need to be addressed.

12.3 Subject Confidentiality

All data (case report forms, recordings, laboratory specimens, and other records) kept at the site will be physically and electronically secured to maintain subject confidentiality. Paper records and computers with subject data will be stored in locked office or cabinet. Computer records will always be password protected, and encrypted when possible. The study database is maintained behind a secure firewall, access is password protected and uses SSL encryption for all data entry and access. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the sponsor, the CCC, the SDMC. the IRB, the FDA, the NINDS, or the OHRP.

12.4 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

13. PUBLICATIONS AND DATA SHARING

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee, and all applicable regulations and rules including reporting to clinicaltrials.gov . Refer to the MoP for further detail.

14. INTEGRATED SUB-STUDIES

Consistent with pre-existing scientific aims of the research team, and with recommendations of peer review and trial oversight groups prior to initiation of the trial, the study leadership will, contingent on funding, fully integrate additional study procedures into the clinical trial protocol in support of specific supplemental aims. As requested, the leadership has pursued ancillary grant support of these aims. These supplemental procedures relate directly to providing a more complete and nuanced explanation of the trial's outcomes, and a better understanding of the underlying mechanisms of treatment response. These integrated sub-study procedures were created to ensure that they not interfere with other study procedures, and have been reviewed and approved by the ESETT Data and Safety Monitoring Board. Sub-study aims and procedures are detailed in the MoP.

14.1 Pharmacokinetics/Pharmacodynamics (PK/PD)

Blood sampling as previously described at section 6.4, is used to determine the plasma levels of study drugs in subjects at a fixed interval after administration. It is anticipated that all sites participate, and that samples are collected from all subjects whenever possible. This sub-study is led by Dr. Lisa Coles, with the advice and assistance of Dr. James Cloyd.

14.2 Emergent Electroencephalography (eEEG)

To characterize the electrographic outcomes of subjects with both clinical treatment success and clinical treatment failure after study drug administration, novel application of simplified EEG technology and procedures is performed and evaluated in a subset of ESETT subjects at a selected number of performance sites. The goal is for eEEG to be acquired as early after enrollment as possible and prior to the primary outcome. Participation of sites is determined by availability of equipment, site accrual rates to date, and site ability to complete the testing. This sub-study is led by Drs. John Betjemann and Brian Litt.

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CONFIDENTIAL

Established Status Epilepticus Treatment Trial (ESETT)
Statistical Analysis Plan
(SAP)

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Version 1

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TABLE OF CONTENTS

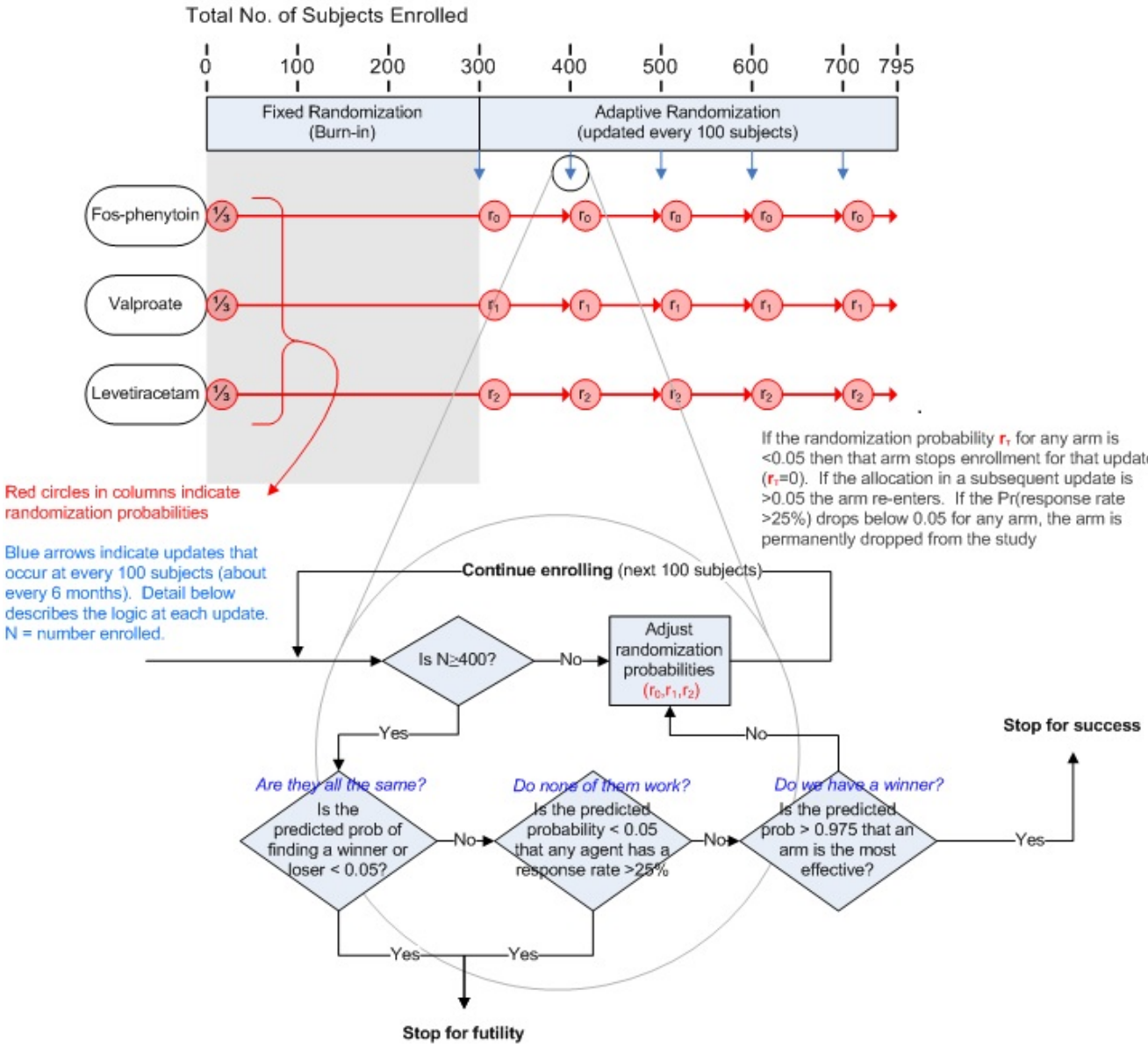
1 LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
DSMB	Data Safety and Monitoring Board
ITT	Intent-to-Treat
NETT	Neurological Emergencies Treatment Trials
NINDS	National Institute of Neurological Disorders and Stroke
SAE	Serious Adverse Event
SDMC	Statistical and Data Management Center

2 OVERVIEW OF THE STUDY DESIGN

This is a multicenter, randomized, blinded, response-adaptive, comparative effectiveness trial of three active treatments in patients with established status epilepticus (ESE) who have failed benzodiazepines. The primary objective is to determine the most effective and/or the least effective treatment of established status epilepticus (ESE) among patients older than 2 years. There are three active treatment arms being compared: fosphenytoin (FOS), levetiracetam (LEV), and valproic acid (VPA). Subjects will initially be randomized equally to all three treatments (1:1:1 ratio). Once 300 subjects are enrolled, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm. Interim analyses are planned after 400, 500, 600 and 700 patients are enrolled. At each interim analysis, there may be updates to the randomization probabilities. At each interim analysis, the trial may stop early for success or futility. The maximum sample size is 795 patients total.

3 SCHEMATIC OF DESIGN



4 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. A patient is considered a treatment success if they meet the definition of the primary outcome as defined above.

5 ANALYSIS SAMPLES

5.1 ITT SAMPLE

The intent-to-treat sample (ITT) includes all unique patients who are randomized, regardless of amount of treatment actually received. Patients who are known to have been enrolled more than once (re-enrollers) will have only their first enrollment included in the primary analysis.Patients are counted as

being a part of the treatment group to which they were given at the time of randomization (defined as when the infusion pump is connected to study drug vial and the patient's IV catheter is switched on). The primary analysis will use the ITT sample.

5.2 PER-PROTOCOL SAMPLE

The per-protocol sample includes all patients who meet the study inclusion criteria and who received at least 80% of the study drug to which they were randomized. Secondary analyses of the primary outcome will use the per-protocol sample.

5.3 RE-ENROLLERS SAMPLE

It is anticipated that a maximum of 5% of subjects will be re-enrolled. The re-enrollers sample includes all patients who are in the ITT sample. Patients who are enrolled more than once will have each enrollment included in this sample. Analyses of safety outcomes will use the re-enrollers sample.

6 RANDOMIZATION

The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject. Throughout the trial, randomization will be stratified by three age groups (<18 years, 18-65 years, and >65 years and older). To ensure similar randomization probabilities across the three age groups while incorporating adaptive randomization, we will use a "Step Forward" centralized randomization procedure developed for emergency treatment trials.[2]

The randomization scheme will be equal allocation (1:1:1) for the first 300 patients. Once 300 subjects are enrolled, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm using information weighting (Connor 2013). Information is a measure of the expected reduction in variance from adding an additional patient to treatment arm t and is defined for treatment arm, t, as $I_t = (p_t \, \mathrm{Var}(\theta_t)/(n_t + 1))^{1/2}$ where p_t is the probability treatment t provides the highest success rate, θ_t is the success rate, and n_t is the number of patients randomized to treatment t. I_t is calculated for all three treatment arms, and the values are rescaled to produce randomization probabilities, r_t for therapy t, for the next 100 patients as $r_t = I_t / \Sigma(I_t)$ that sum to 1. The result is that better treatments are favored, but if at an interim analysis two arms are equally effective, the arm with fewer patients randomized to it will have a larger randomization probability for the next set of patients. The target allocation ratio will be updated every 100 patients.

7 PRIMARY ANALYSIS

This trial will be considered a success if the posterior probability that a treatment is the most effective is greater than 0.975 or the posterior probability that a treatment is the least effective is greater than 0.975. The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods based on a uniform beta prior for each treatment's success rate, and a conjugate beta-binomial model[1]. At the conclusion of the trial, we will report the response rate for each treatment group with 95% credible intervals as well as the pairwise differences in response rates with 95% credible intervals.

Each of the three treatment arms is modeled independently. We assume the probability of success, θ_T, has a prior distribution, $[\theta_T] \sim \text{Beta}(1,1)$ for $T \in \{\text{FOS, LEV, VPA}\}$. We assume the number of observed successes on each treatment, X_T, among the currently enrolled patients on treatment T, N_T, follows a binomial distribution. We will update the prior distribution with the observed data. The posterior distribution for each treatment arm will therefore be $[\theta_T \mid X_T, N_T] \sim \text{Beta}(1+X_T, 1+N_T - X_T)$. The resulting posterior distribution is used to calculate the probability that each treatment is the most effective and the probability that each treatment is the least effective (t_{max} and t_{min}, respectively). The probability treatment T is the best treatment, $\Pr(T = t_{max}) = \Pr(\theta_T > \theta_X \text{ and } \theta_T > \theta_Y)$ where X and Y represent the two treatments other than treatment T. Likewise, the probability treatment T is the least effective treatment, $\Pr(T = t_{min}) = \Pr(\theta_T < \theta_X \text{ and } \theta_T < \theta_Y)$.

The joint posterior for the three response rates is

$$f\left(\theta_{LVT}, \theta_{VPA}, \theta_{fPHT} \mid X_{LVT}, N_{LVT}, X_{VPA}, N_{VPA}, X_{fPHT}, N_{fPHT}\right) = f\left(\theta_{LVT}, \mid X_{LVT}, N_{LVT}\right) f\left(\theta_{VPA}, \mid X_{VPA}, N_{VPA}\right) f\left(\theta_{fPHT}, \mid X_{fPHT}, N_{fPHT}\right)$$

The posterior probability θ_{LVT} is the highest response rate is

$$\Pr(LVT = t_{max}) = \Pr((\theta_{LVT} > \theta_{VPA}) \,\&\, (\theta_{LVT} > \theta_{fPHT}))$$
$$= \int_0^1 \int_0^{\theta_{LVT}} \int_0^{\theta_{LVT}} f(\theta_{LVT}|X_{LVT}, N_{LVT}) f(\theta_{VPA}|X_{VPA}, N_{VPA}) f\left(\theta_{fPHT}|X_{fPHT}, N_{fPHT}\right) d\theta_{fPHT} d\theta_{VPA} d\theta_{LVT}$$

The posterior probability θ_{LVT} is the lowest response rate is

$$\Pr(LVT = t_{min}) = \Pr((\theta_{LVT} < \theta_{VPA}) \,\&\, (\theta_{LVT} < \theta_{fPHT}))$$
$$= \int_0^1 \int_{\theta_{LVT}}^1 \int_{\theta_{LVT}}^1 f(\theta_{LVT}|X_{LVT}, N_{LVT}) f(\theta_{VPA}|X_{VPA}, N_{VPA}) f\left(\theta_{fPHT}|X_{fPHT}, N_{fPHT}\right) d\theta_{fPHT} d\theta_{VPA} d\theta_{LVT}$$

These are similarly specified for VPA and fPHT. This trial will be considered a success if $\Pr(T{=}t_{max}) > 0.975$ and/or $\Pr(T'{=}t_{min}) > 0.975$ for any treatments T and T'. This represents that the trial has identified the best or worst treatment with high probability. Model details have been published[1].

8 INTERIM ANALYSIS

Interim monitoring for success and futility will begin after 400 patients have been enrolled and will be repeated after every additional 100 patients are enrolled. Thus, interim analyses will be performed after 400, 500, 600, and 700 patients. This trial will stop early for success if we have identified the maximum effective treatment with at least 97.5% probability.

There are two early futility criteria. The first futility rule will stop the trial early if all treatment arms have a clinically unacceptable response rate. This trial may stop early for futility if there is a low probability, less than 5%, that any of the three treatment arms is achieving a response rate of at least 25%. The second futility rule will stop the trial early if all treatments are performing similarly and we will be unable to identify a most effective or least effective treatment. This trial will stop early for futility

if the predictive probability of identifying either the most effective or the least effective treatment at the maximum sample size is less than 5%.

All interim analysis results will be considered confidential and only presented to the Data and Safety Monitoring Board in a formal report prepared by the paritally unblinded statistical team at the Statistical and Data Management Center (SDMC). Following review of both the interim analysis results and safety data, the DSMB will make a recommendation regarding the above decisions.

9 GENERAL SAMPLE SIZE CONSIDERATIONS

This study will enroll a maximum total sample size of 795 patients over 4 years, at an accrual rate of approximately 16.5 patients per month. A maximum sample size of 795 provides 90% power to identify the most effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (an absolute difference of 15%). The trial operating characteristics were determined via an extensive simulation study. The statistical and full simulation details as well as the operating characteristics of the design are provided in Appendix and have been published[1].

The expected response rates for FOS, LEV and VPA are based on the retrospective analysis of 279 episodes of ESE in adults, who were treated with PHT, LEV or VPA[3]. The study reported 59.6% of patient episodes responded to FOS, 51.7% to LEV and 74.6% to VPA. Based on this study and expert evaluation of all currently published data on the treatment of ESE, we expect that the worst drug will be effective in 50% of the patients. A 15% difference is the minimum clinically important difference sufficient to change clinical practice.

The total sample size for this trial corresponds to the sample size that would be needed for a frequentist analysis. A sample size of 209/group (627 total) is needed for a χ^2 test with 2 degrees of freedom of the overall test of equality of the three proportions with 90% power (assuming the smallest proportion is 0.50 and the largest proportion is 0.65 and the average proportion is 0.55, two-sided alpha 0.05). For a two-sample test of proportions (all pairwise comparisons of treatment groups), with equal allocation into each treatment group, when one treatment proportion is 0.50 and the other treatment proportion is 0.65, the sample size needed is 240 per group to detect an absolute treatment difference as small as 0.15 with 90% power (assuming two-sided alpha 0.05 and interim looks). Thus, a total sample size of 240*3groups=720 (uninflated for re-enrollers, missing data). Given the possibility of re-enrollers, protocol violations, and missing data, the maximum sample size was inflated from 720 up to 795 by N`=720*R where R=(1/(1-.025)^2)*1.05. The sample size was inflated in two ways[4]. First, for the re-enrollers (expected to be 5%) who will be excluded from the analysis. Secondly, to account for the impact of treatment noncompliance, protocol violations, and missing data on the ITT analysis (expected to occur 2.5% of the time). In order to determine the operating characteristics for this Bayesian adaptive design, simulations were performed assuming a maximum sample size of 720 (the uninflated maximum) and considering different response rate scenarios.

9.1 SIMULATION DETAILS

Table 1. Response Rate Scenarios Considered

	Drug A	Drug B	Drug C
Null	50%	50%	50%
One Good Treatment	50%	50%	65%
Two Good Treatments	50%	65%	65%
One Middle One Good	50%	57.5%	65%
All Bad	25%	25%	25%
All Really Bad	10%	10%	10%

Simulations of the proposed design included 1.) response-adaptive randomization (RAR); 2) frequent interim assessments, 3) a Bayesian approach to identify the most and or least effective treatment. Table 1 shows the response rate scenarios considered in the simulations. To evaluate how the design performs, we simulated the trial (including the response adaptive randomization and interim analysis) considering different success rate scenarios. The operating characteristics are based on *100,000* simulations per scenario. All simulations were programmed in R. Complete details are provided in Appendix. These scenarios illustrate a difference of 7.5% and 15% between drugs.

Table 2 show the trial's operating characteristics for these response rate scenarios including the probability of identifying the most effective treatment (t_{max}) and the probability of identifying the least effective treatment (t_{min}) and the overall probability of trial success (last column).

Table 2. Simulated Operating Characteristics: Power and Type I error Probability (maximum N=720)

Scenario **3 Efficacy Rates**	**Prob** **Drug A** **identified as** t_{max} / t_{min}	**Prob** **Drug B** **identified as** t_{max} / t_{min}	**Prob** **Drug C** **identified as** t_{max} / t_{min}	**Prob** **One Arm is** **identified as** t_{max}/ t_{min}	**Prob Trial** **Success** **(identify** t_{max} **and/or** t_{min}**)**
Null 50% - 50% - 50%	0.005/ 0.005	0.006/ 0.007	0.006/ 0.006	0.017 / 0.021	0.037
One Good 50% - 50% - 65%	0.00/ 0.023	0.00/ 0.010	0.90/ 0	**0.90** / 0.04	0.91
Two Good 50% - 65% - 65%	0.00/ 0.672	0.05/ 0.00	0.05/ 0.00	0.11 / **0.69**	0.77
One Middle One Good 50% - 57.5% - 65%	0.00/ 0.245	0.00/ 0.00	0.49/ 0.00	0.49 / 0.24	**0.68**
All Bad 25% - 25% - 25%	0.005/ 0.006	0.005/ 0.006	0.005/ 0.008	0.016/ 0.020	0.036
All Really Bad 10% - 10% - 10%	0.002 0.002	0.005 0.003	0.001 0.005	0.005 / 0.000	0.005

9.2 POWER

The power or the true positive rate of this trial is the probability of identifying the most effective treatment when one truly exists and/or probability of identifying the least effective treatment when one truly exists. Table 2 shows the power for 3 scenarios in **bold font**. In the "One Good" scenario, one

treatment arm has a 65% response rate compared to a 50% response rate in the other two arms. The power to correctly identify the most effective treatment is 90%. In the "Two Good" scenario, one arm is ineffective (50% response rate) relative to the other two (65% response rate) and the probability of correctly identifying a least effective treatment is 69%. In the "One Middle One Good" scenario, there is a modest treatment effect in one arm and a strong treatment effect in another arm. The power to correctly identify either a most or a least effective treatment (or both) is 68%. The power to identify the best treatment in the One Good and One Middle One Good scenarios exceed the power for the same design with fixed randomization (90% vs. 87% and 49% vs. 45%, respectively).[1]

9.3 TYPE I ERROR PROBABILITY

The type I error probability (false positive rate) of this trial is the probability of incorrectly identifying a most effective treatment and/or incorrectly identifying a least effective treatment. Under simulation, this is determined as the number of trials that incorrectly identify t_{max} and/or t_{min}. Table 2 underlines the type I errors. In the "Null" scenario where all treatment arms have the same 50% response rate, the probability of incorrectly identifying a maximum effective treatment is 0.017 and the probability of incorrectly identifying a least effective treatment is 0.021. The *"familywise"* type I error probability is well controlled (less than 0.05) under the complete null configurations: 0.037 for the "Null" scenario, 0.036 for the "All Bad" scenario, and 0.005 for the "All Really Bad" scenario (Table 2 last column). In the "One Good" scenario, the overall type I error probability is 0.04 and under the "One Middle One Good" scenario, the overall type I error probability is 0.000. In the "Two Good" scenario, two of the treatment arms have the same response rate and the probability of incorrectly identifying one of these good treatments as the most effective is 0.11. Under these simulations, the worst arm was never incorrectly identified as the best, nor was the best arm incorrectly identified as the worst.

Table 3. Mean Allocation (Proportion of Total Mean Allocation)

Scenarios	Total N	Drug A	Drug B	Drug C
Null (50% - 50% - 50%)	508	169 (33%)	169 (33%)	169 (33%)
One Good (50% - 50% - 65%)	484	127 (26%)	127 (26%)	***231 (47%)***
Two Good (50% - 65% - 65%)	684	115 (17%)	***284 (41%)***	***284 (41%)***
One Middle One Good (50%- 57.5%- 65%)	592	123 (22%)	190 (32%)	***279 (47%)***
All Bad (25% - 25% - 25%)	522	174 (33%)	174 (33%)	174 (34%)
All Really Bad (10% - 10% - 10%)	400	133 (33%)	133 (33%)	133 (34%)

Table 3 shows the mean sample size and the mean allocation to each of the three treatment arms for each of the response rate scenarios. The proportion of the total sample size allocated to each arm is shown in parentheses. The most effective treatment arm(s) is shown in bold-italics. Response adaptive allocation (RAR) tends to place a higher proportion of patients on the most effective treatment arm(s). In the scenarios where there is no difference between treatment arms (Null, All Bad, All Really Bad) patients are evenly allocated. In the case with one treatment is 15% better than the other two, the Bayesian adaptive design tends to stop early with an average of 484 patients. In other scenarios, where the drugs are ineffective (all bad or all really bad) or no different from one another, the trial tends to stop early with 400-522 patients enrolled.

In summary, the simulation results show that the proposed design will have high power (90%) for the primary analysis, and the type I error probability is well controlled (less than 0.05) under the complete null scenarios (Null, All Bad, All Really Bad) and under most other treatment configurations considered.

Furthermore, the proposed method of RAR, randomizes more patients to the most effect therapy(-ies) when there truly is a better treatment(s).

9.4 FREQUENTIST ANALYSIS OF THE PRIMARY OUTCOME

At the final analysis, the global null hypothesis $H_0 : \theta_{LVT} = \theta_{VPA} = \theta_{fPHT}$ that the probabilities of success for all three treatment groups are equal will be tested in a chi-squared test with 2 degrees of freedom. If, and only if, the three-way, global null hypothesis is rejected, then all pairwise comparisons will be performed as a two-sample test of difference in proportions (*Z* - test).

Each pairwise null hypothesis of superiority ($H_0 : \theta_{LVT} = \theta_{VPA}$, $H_0 : \theta_{VPA} = \theta_{fPHT}$, and $H_0 : \theta_{LVT} = \theta_{fPHT}$) will be rejected if the p-value for the global null hypothesis is less than 0.01582, and the two-sided p-value for the two-sample test of proportions is less than 0.01582. This approach uses a closed testing procedure to control the type I error rate at alpha under multiple comparisons. Although the Frequentist tests will only occur once, we will use Pocock stopping boundaries to control the overall alpha at 0.05. The corresponding Pocock stopping boundary would be a Z-value of ±2.413 for 5 looks, which corresponds to a two-sided p-value of 0.01582.

Simulations have been conducted to demonstrate that the proposed Frequentist testing approach will control the type I error rate at alpha 0.05 (two-sided). Using the exact data file that was simulated for the Bayesian design, which incorporates the possibility of early stopping, the Frequentist test procedure describe above was applied.

Recall, the simulations of the Bayesian adaptive design included 1.) response-adaptive randomization (RAR); 2) frequent interim assessments, 3) a Bayesian approach to identify the most and or least effective treatment. Simulations were performed assuming a maximum sample size of 720 (the uninflated maximum). The type I error rates are based on *100,000* simulations per scenario.

As can be seen in Table 4, the familywise type I error rate is less than 0.05 for all 4 scenarios considered (***last column, bold italics***). The pairwise type I error rates are underlined above (all $\leq$ 0.01). The remaining values in Table 4 that are neither underlined nor bolded represent the proportion of times the null hypothesis was correctly rejected.

Table 4. Simulated Operating Characteristics (*100,000* simulations): Empirical Type I error Rates for Frequentist Testing Procedure (alpha=0.01582 for Pocock boundary with 5 looks)

	Test of $H_0 : \theta_A = \theta_B$		Test of $H_0 : \theta_B = \theta_c$		Test of $H_0 : \theta_A = \theta_c$		Familywise Type I error rate
Scenarios A% -B% - C%	Proportion of times null rejected* with $\hat{\theta}_A < \hat{\theta}_B$	Proportion of times null rejected* with $\hat{\theta}_A > \hat{\theta}_B$	Proportion of times null rejected* with $\hat{\theta}_B < \hat{\theta}_C$	Proportion of times null rejected* with $\hat{\theta}_B > \hat{\theta}_C$	Proportion of times null rejected* with $\hat{\theta}_A < \hat{\theta}_C$	Proportion of times null rejected* with $\hat{\theta}_A > \hat{\theta}_C$	**Sum of proportion of times pairwise tests were *incorrectly* rejected**
Null 50% - 50% - 50%	0.005	0.005	0.006	0.006	0.006	0.005	***0.034***
One Good Scenario 50% - 50% - 65%	0.006	0.005	0.689	0.000	0.688	0.000	***0.011***
Two Good 50% - 65% - 65%	0.595	0.000	0.012	0.013	0.596	0.000	***0.025***
One Middle One Good 50% - 57.5% - 65%	0.118	0.0001	0.207	0.0002	0.645	0.0000	***0.0003***

Pairwise null hypothesis is rejected if and only if $H_0 : \theta_A = \theta_B = \theta_c$ is also rejected by X^2_2>8.293 (8.293 is the 98.4% percentile of a χ^2_2 distribution) and |z|>2.413.

10 MISSING DATA AND NON-COMPLIANCE

The primary analysis will be analyzed under the intent-to-treat principle (ITT). The ITT evaluable sample will include all subjects who are randomized. In an ITT analysis, missing data and study noncompliance can be problematic. Due to the short term endpoint, minimal missing data is expected for the primary outcome. However, inability to administer the full dose of the study drug or other protocol violations may occur which attenuate the treatment effect. It is anticipated that a maximum of 2.5% of data will be missing or involve noncompliance/protocol violations. Any missing values will be considered a treatment failure.

11 SECONDARY AND EXPLORATORY ANALYSIS OF THE PRIMARY OUTCOME

Secondary analyses of primary outcome will include an analysis of the adjudicated primary outcome, a re-enroller analysis, a per protocol analysis, an analysis by age group. Due to the low amount of re-enrollers expected, the re-enroller analysis will treat repeated assessments from the same individual as if they were independent (naive assumption). If the number of re-enrollers exceeds 10% of the total unique subjects enrolled, then a generalized linear mixed model (assuming the binomial distribution, logit link, random effect for subject) will be fit using the repeated assessments for re-enrollers.

Exploratory analyses of the primary outcome will assess treatment differences adjusting for covariates (see section 12). Secondary and exploratory analyses will not be adjusted for multiple comparisons.

To assess whether there is a change in the response rate over time due to changing perceptions amongst the investigators, we will fit a model with an autoregressive correlation structure (time series) to assess whether the data may be assumed to be i.i.d. It is possible that the overall response rate may increase over time, due to investigators' knowledge of the trial design, repeated unblinding, and investigator bias in ascertaining a treatment response (later cohorts are likely be enrolled to a winning treatment arm, thus response rate is expected to be better for later cohorts than at trial start).

12 COVARIATE ADJUSTMENT

The primary analysis will be unadjusted for baseline covariates. Exploratory analyses of the primary outcome will assess treatment differences adjusting for etiology, time from seizure onset to randomization, age group, and weight (>75 kg and $\leq$75kg). Clinically important differences due to gender, racial, or ethnic differences are not expected, but will be explored. Each covariate is evaluated individually first with a logistic regression model that includes an interaction effect with the treatment. A multivariable logistic model that includes covariates that contributed significantly ($p<0.05$) or are treatment modifiers (interact with treatment group) individually may then be constructed.

13 SITE EFFECTS

Most of the differences expected by enrolling hub/site will be due to the age groups of the patient populations (pediatric patients enrolled at the PECARN site versus all ages enrolled at the NETT hubs). Although we do not anticipate significant hub/site effects, we will investigate potential associations as a secondary analysis of the primary outcome. A generalized linear mixed model with log link function will be fit including treatment group, any covariates found to be significant in section 12, and hub/site as a random effect (SAS PROC NLMIXED).

14 PEDIATRIC SUBGROUP ANALYSIS

Etiology and clinical outcome of status epilepticus are related to age. The etiology is mainly infectious in children and largely due to vascular events and tumors in those older than 65 years. Fospheytoin induced hypotension is more common in those older than 65 years of age. Moreover, mortality increases with age.

At each interim analysis, the interaction of age group and treatment group will be tested using a logistic regression fit with treatment groups, age groups, and the interaction terms of treatment groups and age groups. If there is sufficient evidence that interaction effects are present, defined as p-value<0.05 for the overall test of interaction terms (a Wald χ^2 test with 4 degrees of freedom), then the response adaptive randomization will be stopped and randomization will revert to equal allocation until the end of the trial. Since there is no prior evidence that an interaction exists and given that the test for an interaction will be repeated at each interim analysis, the higher alpha-level of 10% conventionally used for tests of interaction was reduced to 5%. At the end of the trial, a secondary analysis of the primary outcome will be done by age group (children, adult, and Seniors).

The models assessed in sections 12 and 13 will be repeated with the pediatric subgroup.

15 SECONDARY OUTCOMES

15.1 SECONDARY EFFICACY OUTCOMES

Secondary efficacy outcomes include:

- time to termination of seizures
- admission to ICU
- length of ICU and hospital stays

The time to termination of seizures is the interval from the start of infusion of study drug to cessation of clinically apparent seizure in those who meet the primary outcome. Hospital and ICU admission from the ED, and length of stay, is abstracted from the hospital admission record. ICU admission is recorded as occurring only if the ICU is the initial inpatient unit for the patient. Length of stay is determined by the number of calendar days after the day of ED arrival until hospital discharge or subject end-of-study.

15.2 SAFETY OUTCOMES

Primary safety outcome is the absence of life threatening hypotension and cardiac arrhythmia within 60 minutes of the start of study drug infusion. (See protocol for definition of **life-threatening hypotension** and **life-threatening cardiac arrhythmia**).

Other Safety Outcomes:

- Life-threatening hypotension
- Life-threatening cardiac arrhythmia
- Mortality
- Need for endotracheal intubation
- Acute recurrent seizure
- Acute anaphylaxis
- Respiratory depression
- Hepatic transaminase or ammonia elevations
- Purple glove syndrome

Each Closed DSMB report will test for differences in safety events in treatment groups using a chi-squared test. Safety events will also be reported by weight group (>75kg <75kg). Since there are multiple comparisons and multiple looks, the pre-specified level of significance is 0.01.

15.3 ANALYSIS OF SECONDARY OUTCOMES

At the final analysis, the secondary outcomes will be compared by treatment group. All secondary outcomes will be tested at a significance level of two-sided alpha of 0.05. Binary outcomes will be compared by first testing the null hypothesis that the proportion of responses for all three treatment groups are equal in a χ^2 test. If the three-way null hypothesis is rejected, then all pairwise comparisons

will be performed as two-sample tests of proportions. Continuous outcomes will be compared in an F-test to test the null hypothesis that all three treatment groups are equal, followed by pairwise t-tests. The Richmond agitation and sedation score (RASS) at 60 minutes will be compared by treatment groups in a Kruskal-Wallis test. The secondary outcomes will also be compared by treatment group within age group. Kaplan Meier curves and log rank tests will be used to compare time to event outcomes by treatment group. Since mortality is expected to increase by age, a cox proportional hazard model will be used to estimate the hazard ratio and 95% CI for the treatment groups adjusting for age groups and age by treatment interaction terms. If the assumptions for the cox proportional hazard model are not met, Kaplan Meier curves and log rank tests will be used to compare time to mortality by treatment group within each age group.

15.4 SAFETY MONITORING

Active monitoring for all adverse events (AEs) will occur throughout the study by the Data Safety Monitoring Board (DSMB) and as further described in the Safety Monitoring Plan.

16 SCENARIOS

16.1 ANALYSIS SAMPLES

SCENARIO	ITT SAMPLE	PP SAMPLE	RE-ENROLLER SAMPLE
Infusion pump/Catheter turned on	X	X	X
Infusion was stopped after 2 minutes (patient received less than 80% of study drug)	X		X
Patient did not met eligibility criteria	X		X
Patient was 20 years old, but received the pediatric use next box (e.g. age estimated incorrectly or the adult use next box was missing).	X*	X*	X*
Patient was previously enrolled	**	**	X

*In the analysis, the patient is classified in actual/true age strata and classified in the treatment group they actually received.
**Only the first enrollment is included in the analysis.

16.2 TARGET RANDOMIZATION UPDATES

The target randomization probabilities will be updated based on the primary efficacy outcome (section 4) using the methodology described under section 6. In addition, the randomization probabilities will also be calculated for using a composite outcome of the primary efficacy and primary safety outcome: seizure cessation [as defined in section 4] and the absence of both life-threatening hypotension and life-threatening cardiac arrhythmia. The rationale for the presentation of both sets of randomization

probabilities is life-threatening hypotension and life-threatening cardiac arrhythmia are expected for fosphenytion.

The trial operating characteristics (power and type I error rate) are dependent on carefully following the pre-specified timing of randomization updates and the early stopping rules. Unlike some trials in which there is leeway in the number and timing of interim looks, this design is planned to have fixed adaptations. However, it is possible that a planned adaptation may be unacceptable. It may result in an allocation ratio that is deterministic (e.g. all or nearly all patients are randomized into a single arm). It may be in conflict with the safety profile for a drug (either overall or for a subgroup such as age or weight). Prior to implementing the updated allocation probabilities, the DSMB/DSMB Chair will be asked to review and approve them.

Example of Updated Allocation Probabilities after 300 patients are enrolled:

	N Enrolled								
	Observed Response Rate (Primary Outcome)			Probability that a treatment is the most effective			Updated Randomization Probabilities (r_t)		
Look	**FOS**	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**
	51/99	55/100	64/101						
300	52%	55%	63%	0.025	0.092	0.88	0.12	0.22	0.66

16.3 SCENARIOS IN WHICH THE BEST ARM HAS SAFETY CONCERNS

Scenario	N Enrolled Observed Response Rate: Efficacy			N Enrolled Observed Response Rate: Safety			Updated Randomization Probabilities for Primary Efficacy Outcome (r_t)			Updated Randomization Probabilities for Composite of Efficacy & Safety Outcomes (r_t)			Conclusions
	FOS	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**	
1	50%	45%	35%	10%	0%	0%	0.6	0.34	0.06	0.44	0.45	0.1	Use r_t based on composite outcome
2	50%	45%	40%	5%	0%	0%	0.56	0.31	0.14	0.45	0.37	0.18	Use the r_t based on the primary efficacy outcome
3	55%	55%	50%	5%	0%	0%	0.39	0.41	0.2	0.33	0.44	0.23	Use the r_t based on the primary composite outcome.
4	15%	20%	40%	0%	0%	0%	0	0	1	0	0	1	Stop and declare a winner if Probability that VPA is best is $\geq$0.975. Else randomize 9:1 to VPA & LVT.

1 REFERENCES

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2. Zhao W, Ciolino J, Palesch Y. Step-forward randomization in multicenter emergency treatment clinical trials. *Academic Emergency Medicine*. 2010; Vol 17 No. 6, 659-665. PMID: 20624149, PMC3052925.

3. Alvarez, V, Januel, JM, Burnand, B, et al. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia. 2011; 52:1292-1296.

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2 APPENDIX

DESIGN DOCUMENT FROM BERRY CONSULTANTS

CONFIDENTIAL

Established Status Epilepticus Treatment Trial (ESETT)
Statistical Analysis Plan
(SAP)

Prepared by

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Version 4

May 2018

Summary of Changes

Version 2 Jan 2016

Section 5.1 Edited language defining enrollment/randomization to be “defined as when study drug vial is connected to the patient’s IV and the pump is switched on”.

Section 5.3 Clarified that the re-enroller sample includes “all enrollments of all patients”.

Section 6 & 14 Children was defined as 2-17 rather than <18. Seniors was defined as “66 years and older” rather than >65. The rationale was to clarify how age (a continuous numeric field) would be split.

Section 9 The word “non-compliance” was changed to “cross-overs”. This trial will not have “non-compliance” in the typical sense since patients are actively seizing while study drug is administered.

Section 11 Added a sentence stating “Visual and exploratory analyses of the subset of patients who re-enroll will be done as appropriate (Meurer 2015).”

Section 12 moved the = sign to >=75 rather than <=75 kg.

Section 16.2 and 16.3 scenarios were deleted and left to the discretion of the DSMB.

Reference number 5 was added.

Version 3 Jan 2017

Section 4. Added text under primary outcome to describe how the outcome is to be derived from the Case Report Form Data. “The primary outcome is defined by Form501:Treatment Effect. A patient is a treatment failure if Q07=Yes or Q08=No or Q10=Yes. The entry for "date/time of the 60 minute assessment” reported in Q06 may not be exactly 60 minutes, but the responses to Q07 and Q08 are to be assumed to be implicitly referring to exactly 60 minutes (not the entry of the time of assessment). Thus, there is no need to define “out of window” assessments based on Q06.”

Section 10 added sentences “Safety analysis will include all enrollments of all subjects (including re-enrollments). Subjects with missing/unknown safety events will be considered to have had the event.”

Section 14 test of the interaction with age group will be for <18 versus ≥18 (not all 3 age groups) and the test is a DF=2 not 4. Added a sentence about an exploratory analysis of age as a continuous measure.

Section 15.2 and 15.3 Updated binary test for secondary outcomes will be Fisher’s exact test if frequencies are too small for Chi-squared test.

Version 4 May 2018

ADDED APPENDIX 3 (ENROLLMENT OF CHILDREN ONLY AND MONITORING PLAN FOR PEDIATRIC POPULATION)

Section 8. Added a sentence to clarify that the predictive probability rules for monitoring pediatric population will assume a maximum of N=350 children enrollments.

TABLE OF CONTENTS

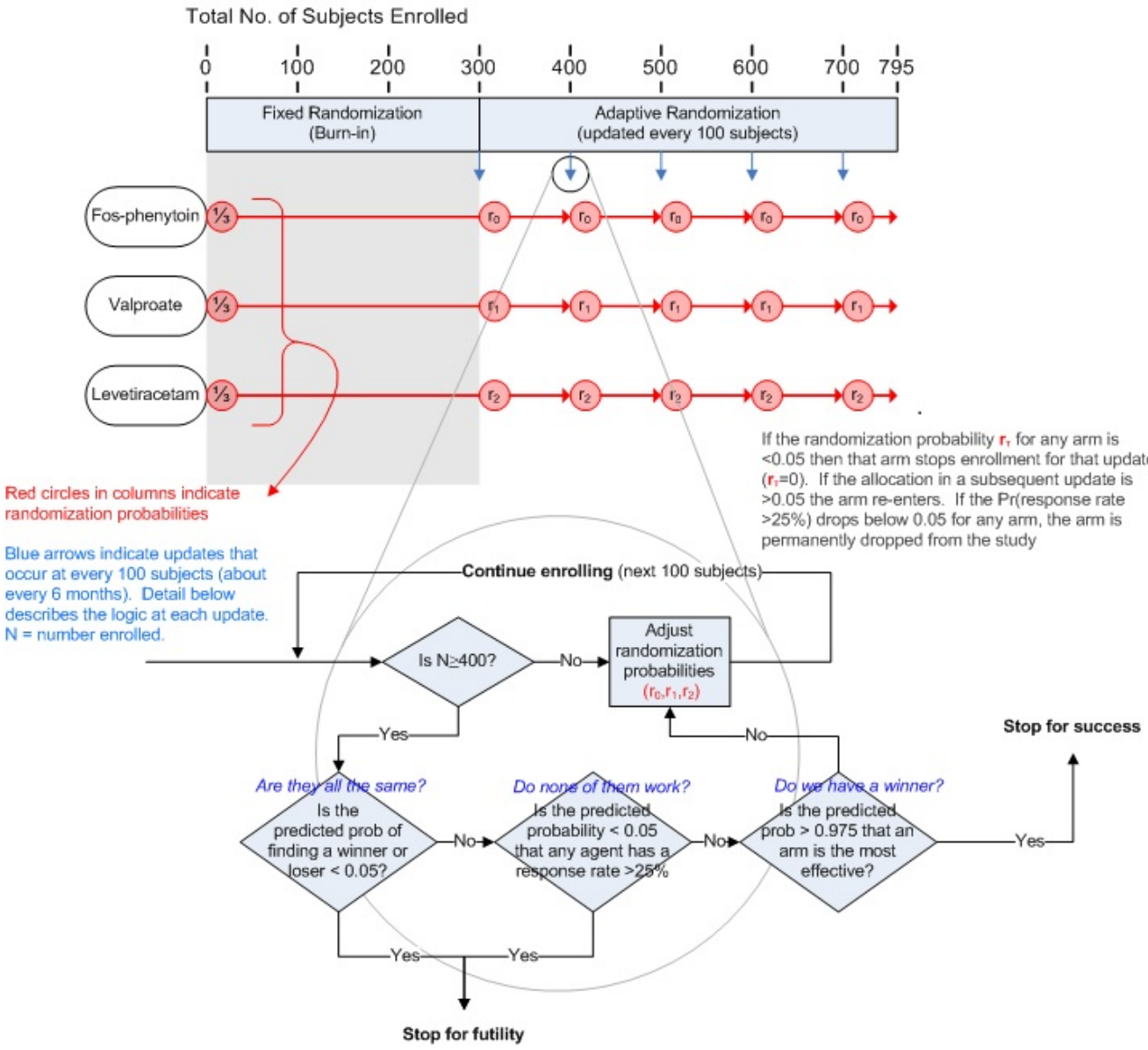
1 LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
DSMB	Data Safety and Monitoring Board
ITT	Intent-to-Treat
NETT	Neurological Emergencies Treatment Trials
NINDS	National Institute of Neurological Disorders and Stroke
SAE	Serious Adverse Event
SDMC	Statistical and Data Management Center

2 OVERVIEW OF THE STUDY DESIGN

This is a multicenter, randomized, blinded, response-adaptive, comparative effectiveness trial of three active treatments in patients with established status epilepticus (ESE) who have failed benzodiazepines. The primary objective is to determine the most effective and/or the least effective treatment of established status epilepticus (ESE) among patients older than 2 years. There are three active treatment arms being compared: fosphenytoin (FOS), levetiracetam (LEV), and valproic acid (VPA). Subjects will initially be randomized equally to all three treatments (1:1:1 ratio). Once 300 subjects are enrolled, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm. Interim analyses are planned after 400, 500, 600 and 700 patients are enrolled. At each interim analysis, there may be updates to the randomization probabilities. At each interim analysis, the trial may stop early for success or futility. The maximum sample size is 795 patients total.

3 SCHEMATIC OF DESIGN



4 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. A patient is considered a treatment success if they meet the definition of the primary outcome as defined above.

The primary outcome is defined by Form501:Treatment Effect. A patient is a treatment failure if Q07=Yes or Q08=No or Q10=Yes. The entry for "date/time of the 60 minute assessment" reported in Q06 may not be exactly 60 minutes, but the responses to Q07 and Q08 are to be assumed to be implicitly referring to exactly 60 minutes (not the entry of the time of assessment). Thus, there is no need to define "out of window" assessments based on Q06.

5 ANALYSIS SAMPLES

5.1 ITT SAMPLE

The intent-to-treat sample (ITT) includes all unique patients who are randomized, regardless of amount of treatment actually received. Patients who are known to have been enrolled more than once (re-enrollers) will have only their first enrollment included. Patients are counted as being a part of the treatment group to which they were given at the time of enrollment/randomization (defined as when study drug vial is connected to the patient's IV and the pump is switched on). The primary analysis will use the ITT sample.

5.2 PER-PROTOCOL SAMPLE

The per-protocol sample includes all patients who meet the study inclusion criteria and who received at least 80% of the study drug to which they were randomized. Secondary analyses of the primary outcome will use the per-protocol sample.

5.3 RE-ENROLLERS SAMPLE

It is anticipated that a maximum of 5% of subjects will be re-enrolled. The re-enrollers sample includes all enrollments of all patients. Patients who are enrolled more than once will have each enrollment included in this sample. Analyses of safety outcomes will use the re-enrollers sample.

6 RANDOMIZATION

The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject. Throughout the trial, randomization will be stratified by three age groups (2-17 years, 18-65 years, and 66 years and older). To ensure similar randomization probabilities across the three age groups while incorporating adaptive randomization, we will use a "Step Forward" centralized randomization procedure developed for emergency treatment trials.[2]

The randomization scheme will be equal allocation (1:1:1) for the first 300 patients. Once 300 subjects are enrolled, response-adaptive randomization (RAR) will be utilized with the goal of maximizing the likelihood of identifying the most effective treatment arm using information weighting (Connor 2013). Information is a measure of the expected reduction in variance from adding an additional patient to treatment arm t and is defined for treatment arm, t, as $I_t = (p_t \, \mathrm{Var}(\theta_t)/(n_t + 1))^{1/2}$ where p_t is the probability treatment t provides the highest success rate, θ_t is the success rate, and n_t is the number of patients randomized to treatment t. I_t is calculated for all three treatment arms, and the values are rescaled to produce randomization probabilities, r_t for therapy t, for the next 100 patients as $r_t = I_t / \Sigma(I_t)$ that sum to 1. The result is that better treatments are favored, but if at an interim analysis two arms are equally effective, the arm with fewer patients randomized to it will have a larger randomization probability for the next set of patients. The target allocation ratio will be updated every 100 patients.

7 PRIMARY ANALYSIS

This trial will be considered a success if the posterior probability that a treatment is the most effective is greater than 0.975 or the posterior probability that a treatment is the least effective is greater than 0.975. The posterior probabilities that each treatment is the most and least effective treatment will be calculated using Bayesian methods based on a uniform beta prior for each treatment's success rate, and a conjugate beta-binomial model[1]. At the conclusion of the trial, we will report the response rate for each treatment group with 95% credible intervals as well as the pairwise differences in response rates with 95% credible intervals.

Each of the three treatment arms is modeled independently. We assume the probability of success, θ_T, has a prior distribution, $[\theta_T] \sim \text{Beta}(1,1)$ for $T \in \{\text{FOS, LEV, VPA}\}$. We assume the number of observed successes on each treatment, X_T, among the currently enrolled patients on treatment T, N_T, follows a binomial distribution. We will update the prior distribution with the observed data. The posterior distribution for each treatment arm will therefore be $[\theta_T \mid X_T, N_T] \sim \text{Beta}(1+X_T, 1+N_T - X_T)$. The resulting posterior distribution is used to calculate the probability that each treatment is the most effective and the probability that each treatment is the least effective (t_{max} and t_{min}, respectively). The probability treatment T is the best treatment, $\Pr(T = t_{max}) = \Pr(\theta_T > \theta_X \text{ and } \theta_T > \theta_Y)$ where X and Y represent the two treatments other than treatment T. Likewise, the probability treatment T is the least effective treatment, $\Pr(T = t_{min}) = \Pr(\theta_T < \theta_X \text{ and } \theta_T < \theta_Y)$.

The joint posterior for the three response rates is

$$f\left(\theta_{LVT}, \theta_{VPA}, \theta_{fPHT} \mid X_{LVT}, N_{LVT}, X_{VPA}, N_{VPA}, X_{fPHT}, N_{fPHT}\right) = f\left(\theta_{LVT}, \mid X_{LVT}, N_{LVT}\right) f\left(\theta_{VPA}, \mid X_{VPA}, N_{VPA}\right) f\left(\theta_{fPHT}, \mid X_{fPHT}, N_{fPHT}\right)$$

The posterior probability θ_{LVT} is the highest response rate is

$$\begin{aligned}\Pr(LVT = t_{max}) &= \Pr((\theta_{LVT} > \theta_{VPA}) \,\&\, (\theta_{LVT} > \theta_{fPHT})) \\ &= \int_0^1 \int_0^{\theta_{LVT}} \int_0^{\theta_{LVT}} f(\theta_{LVT}|X_{LVT}, N_{LVT}) f(\theta_{VPA}|X_{VPA}, N_{VPA}) f\left(\theta_{fPHT}|X_{fPHT}, N_{fPHT}\right) d\theta_{fPHT} d\theta_{VPA} d\theta_{LVT}\end{aligned}$$

The posterior probability θ_{LVT} is the lowest response rate is

$$\begin{aligned}\Pr(LVT = t_{min}) &= \Pr((\theta_{LVT} < \theta_{VPA}) \,\&\, (\theta_{LVT} < \theta_{fPHT})) \\ &= \int_0^1 \int_{\theta_{LVT}}^1 \int_{\theta_{LVT}}^1 f(\theta_{LVT}|X_{LVT}, N_{LVT}) f(\theta_{VPA}|X_{VPA}, N_{VPA}) f\left(\theta_{fPHT}|X_{fPHT}, N_{fPHT}\right) d\theta_{fPHT} d\theta_{VPA} d\theta_{LVT}\end{aligned}$$

These are similarly specified for VPA and fPHT. This trial will be considered a success if $\Pr(T{=}t_{max}) > 0.975$ and/or $\Pr(T'{=}t_{min}) > 0.975$ for any treatments T and T'. This represents that the trial has identified the best or worst treatment with high probability. Model details have been published[1].

8 INTERIM ANALYSIS

Interim monitoring for success and futility will begin after 400 patients have been enrolled and will be repeated after every additional 100 patients are enrolled. Thus, interim analyses will be performed after

400, 500, 600, and 700 patients. This trial will stop early for success if we have identified the maximum effective treatment with at least 97.5% probability.

There are two early futility criteria. The first futility rule will stop the trial early if all treatment arms have a clinically unacceptable response rate. This trial may stop early for futility if there is a low probability, less than 5%, that any of the three treatment arms is achieving a response rate of at least 25%. The second futility rule will stop the trial early if all treatments are performing similarly and we will be unable to identify a most effective or least effective treatment. This trial will stop early for futility if the predictive probability of identifying either the most effective or the least effective treatment at the maximum sample size is less than 5%. The predictive probability rules for monitoring pediatric population will assume a maximum of N=350 children enrollments.

All interim analysis results will be considered confidential and only presented to the Data and Safety Monitoring Board in a formal report prepared by the paritally unblinded statistical team at the Statistical and Data Management Center (SDMC). Following review of both the interim analysis results and safety data, the DSMB will make a recommendation regarding the above decisions.

9 GENERAL SAMPLE SIZE CONSIDERATIONS

This study will enroll a maximum total sample size of 795 patients over 4 years, at an accrual rate of approximately 16.5 patients per month. A maximum sample size of 795 provides 90% power to identify the most effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms (an absolute difference of 15%). The trial operating characteristics were determined via an extensive simulation study. The statistical and full simulation details as well as the operating characteristics of the design are provided in Appendix and have been published[1].

The expected response rates for FOS, LEV and VPA are based on the retrospective analysis of 279 episodes of ESE in adults, who were treated with PHT, LEV or VPA[3]. The study reported 59.6% of patient episodes responded to FOS, 51.7% to LEV and 74.6% to VPA. Based on this study and expert evaluation of all currently published data on the treatment of ESE, we expect that the worst drug will be effective in 50% of the patients. A 15% difference is the minimum clinically important difference sufficient to change clinical practice.

The total sample size for this trial corresponds to the sample size that would be needed for a frequentist analysis. A sample size of 209/group (627 total) is needed for a χ^2 test with 2 degrees of freedom of the overall test of equality of the three proportions with 90% power (assuming the smallest proportion is 0.50 and the largest proportion is 0.65 and the average proportion is 0.55, two-sided alpha 0.05). For a two-sample test of proportions (all pairwise comparisons of treatment groups), with equal allocation into each treatment group, when one treatment proportion is 0.50 and the other treatment proportion is 0.65, the sample size needed is 240 per group to detect an absolute treatment difference as small as 0.15 with 90% power (assuming two-sided alpha 0.05 and interim looks). Thus, a total sample size of 240*3groups=720 (uninflated for re-enrollers, missing data). Given the possibility of re-enrollers, protocol violations, and missing data, the maximum sample size was inflated from 720 up to 795 by

N`=720*R where R=(1/(1-.025)^2)*1.05. The sample size was inflated in two ways[4]. First, for the re-enrollers (expected to be 5%) who will be excluded from the analysis. Secondly, it was inflated to account for the impact of treatment cross-overs, protocol violations, and missing data on the ITT analysis (expected to occur 2.5% of the time). In order to determine the operating characteristics for this Bayesian adaptive design, simulations were performed assuming a maximum sample size of 720 (the uninflated maximum) and considering different response rate scenarios.

9.1 SIMULATION DETAILS

Table 1. Response Rate Scenarios Considered

	Drug A	Drug B	Drug C
Null	50%	50%	50%
One Good Treatment	50%	50%	65%
Two Good Treatments	50%	65%	65%
One Middle One Good	50%	57.5%	65%
All Bad	25%	25%	25%
All Really Bad	10%	10%	10%

Simulations of the proposed design included 1.) response-adaptive randomization (RAR); 2) frequent interim assessments, 3) a Bayesian approach to identify the most and or least effective treatment. Table 1 shows the response rate scenarios considered in the simulations. To evaluate how the design performs, we simulated the trial (including the response adaptive randomization and interim analysis) considering different success rate scenarios. The operating characteristics are based on *100,000* simulations per scenario. All simulations were programmed in R. Complete details are provided in Appendix. These scenarios illustrate a difference of 7.5% and 15% between drugs.

Table 2 show the trial's operating characteristics for these response rate scenarios including the probability of identifying the most effective treatment (t_{max}) and the probability of identifying the least effective treatment (t_{min}) and the overall probability of trial success (last column).

Table 2. Simulated Operating Characteristics: Power and Type I error Probability (maximum N=720)

Scenario 3 Efficacy Rates	**Prob Drug A identified as** t_{max} / t_{min}	**Prob Drug B identified as** t_{max} / t_{min}	**Prob Drug C identified as** t_{max} / t_{min}	**Prob One Arm is identified as** t_{max}/ t_{min}	**Prob Trial Success (identify** t_{max} **and/or** t_{min}**)**
Null 50% - 50% - 50%	0.005/ 0.005	0.006/ 0.007	0.006/ 0.006	0.017 / 0.021	0.037
One Good 50% - 50% - 65%	0.00/ 0.023	0.00/ 0.010	0.90/ 0	**0.90** / 0.04	0.91
Two Good 50% - 65% - 65%	0.00/ 0.672	0.05/ 0.00	0.05/ 0.00	0.11 / **0.69**	0.77

One Middle One Good 50% - 57.5% - 65%	0.00/ 0.245	0.00/ 0.00	0.49/ 0.00	0.49 / 0.24	**0.68**
All Bad 25% - 25% - 25%	0.005/ 0.006	0.005/ 0.006	0.005/ 0.008	0.016/ 0.020	0.036
All Really Bad 10% - 10% - 10%	0.002 0.002	0.005 0.003	0.001 0.005	0.005 / 0.000	0.005

9.2 POWER

The power or the true positive rate of this trial is the probability of identifying the most effective treatment when one truly exists and/or probability of identifying the least effective treatment when one truly exists. Table 2 shows the power for 3 scenarios in **bold font**. In the "One Good" scenario, one treatment arm has a 65% response rate compared to a 50% response rate in the other two arms. The power to correctly identify the most effective treatment is 90%. In the "Two Good" scenario, one arm is ineffective (50% response rate) relative to the other two (65% response rate) and the probability of correctly identifying a least effective treatment is 69%. In the "One Middle One Good" scenario, there is a modest treatment effect in one arm and a strong treatment effect in another arm. The power to correctly identify either a most or a least effective treatment (or both) is 68%. The power to identify the best treatment in the One Good and One Middle One Good scenarios exceed the power for the same design with fixed randomization (90% vs. 87% and 49% vs. 45%, respectively).[1]

9.3 TYPE I ERROR PROBABILITY

The type I error probability (false positive rate) of this trial is the probability of incorrectly identifying a most effective treatment and/or incorrectly identifying a least effective treatment. Under simulation, this is determined as the number of trials that incorrectly identify t_{max} and/or t_{min}. Table 2 underlines the type I errors. In the "Null" scenario where all treatment arms have the same 50% response rate, the probability of incorrectly identifying a maximum effective treatment is 0.017 and the probability of incorrectly identifying a least effective treatment is 0.021. The *"familywise"* type I error probability is well controlled (less than 0.05) under the complete null configurations: 0.037 for the "Null" scenario, 0.036 for the "All Bad" scenario, and 0.005 for the "All Really Bad" scenario (Table 2 last column). In the "One Good" scenario, the overall type I error probability is 0.04 and under the "One Middle One Good" scenario, the overall type I error probability is 0.000. In the "Two Good" scenario, two of the treatment arms have the same response rate and the probability of incorrectly identifying one of these good treatments as the most effective is 0.11. Under these simulations, the worst arm was never incorrectly identified as the best, nor was the best arm incorrectly identified as the worst.

Table 3. Mean Allocation (Proportion of Total Mean Allocation)

Scenarios	Total N	Drug A	Drug B	Drug C
Null (50% - 50% - 50%)	508	169 (33%)	169 (33%)	169 (33%)
One Good (50% - 50% - 65%)	484	127 (26%)	127 (26%)	***231 (47%)***
Two Good (50% - 65% - 65%)	684	115 (17%)	***284 (41%)***	***284 (41%)***
One Middle One Good (50%- 57.5%- 65%)	592	123 (22%)	190 (32%)	***279 (47%)***
All Bad (25% - 25% - 25%)	522	174 (33%)	174 (33%)	174 (34%)
All Really Bad (10% - 10% - 10%)	400	133 (33%)	133 (33%)	133 (34%)

Table 3 shows the mean sample size and the mean allocation to each of the three treatment arms for each of the response rate scenarios. The proportion of the total sample size allocated to each arm is

shown in parentheses. The most effective treatment arm(s) is shown in bold-italics. Response adaptive allocation (RAR) tends to place a higher proportion of patients on the most effective treatment arm(s). In the scenarios where there is no difference between treatment arms (Null, All Bad, All Really Bad) patients are evenly allocated. In the case with one treatment is 15% better than the other two, the Bayesian adaptive design tends to stop early with an average of 484 patients. In other scenarios, where the drugs are ineffective (all bad or all really bad) or no different from one another, the trial tends to stop early with 400-522 patients enrolled.

In summary, the simulation results show that the proposed design will have high power (90%) for the primary analysis, and the type I error probability is well controlled (less than 0.05) under the complete null scenarios (Null, All Bad, All Really Bad) and under most other treatment configurations considered. Furthermore, the proposed method of RAR, randomizes more patients to the most effect therapy(-ies) when there truly is a better treatment(s).

9.4 FREQUENTIST ANALYSIS OF THE PRIMARY OUTCOME

At the final analysis, the global null hypothesis $H_0 : \theta_{LVT} = \theta_{VPA} = \theta_{fPHT}$ that the probabilities of success for all three treatment groups are equal will be tested in a chi-squared test with 2 degrees of freedom. If, and only if, the three-way, global null hypothesis is rejected, then all pairwise comparisons will be performed as a two-sample test of difference in proportions (*Z* - test).

Each pairwise null hypothesis of superiority ($H_0 : \theta_{LVT} = \theta_{VPA}$, $H_0 : \theta_{VPA} = \theta_{fPHT}$, and $H_0 : \theta_{LVT} = \theta_{fPHT}$) will be rejected if the p-value for the global null hypothesis is less than 0.01582, and the two-sided p-value for the two-sample test of proportions is less than 0.01582. This approach uses a closed testing procedure to control the type I error rate at alpha under multiple comparisons. Although the Frequentist tests will only occur once, we will use Pocock stopping boundaries to control the overall alpha at 0.05. The corresponding Pocock stopping boundary would be a Z-value of ±2.413 for 5 looks, which corresponds to a two-sided p-value of 0.01582.

Simulations have been conducted to demonstrate that the proposed Frequentist testing approach will control the type I error rate at alpha 0.05 (two-sided). Using the exact data file that was simulated for the Bayesian design, which incorporates the possibility of early stopping, the Frequentist test procedure describe above was applied.

Recall, the simulations of the Bayesian adaptive design included 1.) response-adaptive randomization (RAR); 2) frequent interim assessments, 3) a Bayesian approach to identify the most and or least effective treatment. Simulations were performed assuming a maximum sample size of 720 (the uninflated maximum). The type I error rates are based on *100,000* simulations per scenario.

As can be seen in Table 4, the familywise type I error rate is less than 0.05 for all 4 scenarios considered (***last column, bold italics***). The pairwise type I error rates are underlined above (all $\leq$ 0.01). The remaining values in Table 4 that are neither underlined nor bolded represent the proportion of times the null hypothesis was correctly rejected.

Table 4. Simulated Operating Characteristics (*100,000* simulations): Empirical Type I error Rates for Frequentist Testing Procedure (alpha=0.01582 for Pocock boundary with 5 looks)

	Test of $H_0: \theta_A = \theta_B$		Test of $H_0: \theta_B = \theta_c$		Test of $H_0: \theta_A = \theta_c$		Familywise Type I error rate
Scenarios A% -B% - C%	Proportion of times null rejected* with $\hat{\theta}_A < \hat{\theta}_B$	Proportion of times null rejected* with $\hat{\theta}_A > \hat{\theta}_B$	Proportion of times null rejected* with $\hat{\theta}_B < \hat{\theta}_C$	Proportion of times null rejected* with $\hat{\theta}_B > \hat{\theta}_C$	Proportion of times null rejected* with $\hat{\theta}_A < \hat{\theta}_C$	Proportion of times null rejected* with $\hat{\theta}_A > \hat{\theta}_C$	**Sum of proportion of times pairwise tests were *incorrectly* rejected**
Null 50% - 50% - 50%	0.005	0.005	0.006	0.006	0.006	0.005	***0.034***
One Good Scenario 50% - 50% - 65%	0.006	0.005	0.689	0.000	0.688	0.000	***0.011***
Two Good 50% - 65% - 65%	0.595	0.000	0.012	0.013	0.596	0.000	***0.025***
One Middle One Good 50% - 57.5% - 65%	0.118	0.0001	0.207	0.0002	0.645	0.0000	***0.0003***

Pairwise null hypothesis is rejected if and only if $H_0: \theta_A = \theta_B = \theta_c$ is also rejected by $X^2_2 > 8.293$ (8.293 is the 98.4% percentile of a χ^2_2 distribution) and $|z| > 2.413$.

10 MISSING DATA AND NON-COMPLIANCE

The primary analysis will be analyzed under the intent-to-treat principle (ITT). The ITT evaluable sample will include all subjects who are randomized. In an ITT analysis, missing data and study noncompliance can be problematic. Due to the short term endpoint, minimal missing data is expected for the primary outcome. However, inability to administer the full dose of the study drug or other protocol violations may occur which attenuate the treatment effect. It is anticipated that a maximum of 2.5% of data will be missing or involve noncompliance/protocol violations. Any missing values for the primary outcome will be considered a treatment failure. Safety analysis will include all enrollments of all subjects (including re-enrollments). Subjects with missing/unknown safety events will be considered to have had the event.

11 SECONDARY AND EXPLORATORY ANALYSIS OF THE PRIMARY OUTCOME

Secondary analyses of primary outcome will include an analysis of the adjudicated primary outcome, a re-enroller analysis, a per protocol analysis, an analysis by age group. Due to the low amount of re-enrollers expected, the re-enroller analysis will treat repeated assessments from the same individual as if they were independent (naive assumption). If the number of re-enrollers exceeds 10% of the total unique subjects enrolled, then a generalized linear mixed model (assuming the binomial distribution, logit link, random effect for subject) will be fit using the repeated assessments for re-enrollers. Visual and exploratory analyses of the subset of patients who re-enroll will be done as appropriate (Meurer

2015). Exploratory analyses of the primary outcome will assess treatment differences adjusting for covariates (see section 12). Secondary and exploratory analyses will not be adjusted for multiple comparisons.

To assess whether there is a change in the response rate over time due to changing perceptions amongst the investigators, we will fit a model with an autoregressive correlation structure (time series) to assess whether the data may be assumed to be i.i.d. It is possible that the overall response rate may increase over time, due to investigators' knowledge of the trial design, repeated unblinding, and investigator bias in ascertaining a treatment response (later cohorts are likely be enrolled to a winning treatment arm, thus response rate is expected to be better for later cohorts than at trial start).

12 COVARIATE ADJUSTMENT

The primary analysis will be unadjusted for baseline covariates. Exploratory analyses of the primary outcome will assess treatment differences adjusting for etiology, time from seizure onset to randomization, age group, and weight (< 75kg or $\geq$75 kg). Clinically important differences due to gender, racial, or ethnic differences are not expected, but will be explored. Each covariate is evaluated individually first with a logistic regression model that includes an interaction effect with the treatment. A multivariable logistic model that includes covariates that contributed significantly ($p<0.05$) or are treatment modifiers (interact with treatment group) individually may then be constructed.

13 SITE EFFECTS

Most of the differences expected by enrolling hub/site will be due to the age groups of the patient populations (pediatric patients enrolled at the PECARN site versus all ages enrolled at the NETT hubs). Although we do not anticipate significant hub/site effects, we will investigate potential associations as a secondary analysis of the primary outcome. A generalized linear mixed model with log link function will be fit including treatment group, any covariates found to be significant in section 12, and hub/site as a random effect (SAS PROC NLMIXED).

14 PEDIATRIC SUBGROUP ANALYSIS

Etiology and clinical outcome of status epilepticus are related to age. The etiology is mainly infectious in children and largely due to vascular events and tumors in those older than 65 years. Fosphenytoin induced hypotension is more common in those older than 65 years of age. Moreover, mortality increases with age.

At each interim analysis, the interaction of age group (<18 versus $\geq$18) and treatment group will be tested using a logistic regression fit with treatment groups, age group, and the interaction terms of treatment groups and age group. If there is sufficient evidence that interaction effects are present, defined as p-value<0.05 for the overall test of interaction terms (a Wald χ^2 test with 2 degrees of freedom), then the response adaptive randomization will be stopped and randomization will revert to equal allocation until the end of the trial. Since there is no prior evidence that an interaction exists and given that the test for an interaction will be repeated at each interim analysis, the higher alpha-level of 10% conventionally used for tests of interaction was reduced to 5%. At the end of the trial, a secondary analysis of the primary outcome will be done by age group (2-17 years, 18-65 years, and 66 and older). Exploratory analyses will consider the effect of age as a continuous measure as well as cutpoints.

The models assessed in sections 12 and 13 will be repeated with the pediatric subgroup.

15 SECONDARY OUTCOMES

15.1 SECONDARY EFFICACY OUTCOMES

Secondary efficacy outcomes include:

- time to termination of seizures
- admission to ICU
- length of ICU and hospital stays

The time to termination of seizures is the interval from the start of infusion of study drug to cessation of clinically apparent seizure in those who meet the primary outcome. Hospital and ICU admission from the ED, and length of stay, is abstracted from the hospital admission record. ICU admission is recorded as occurring only if the ICU is the initial inpatient unit for the patient. Length of stay is determined by the number of calendar days after the day of ED arrival until hospital discharge or subject end-of-study.

15.2 SAFETY OUTCOMES

Primary safety outcome is the absence of life threatening hypotension and cardiac arrhythmia within 60 minutes of the start of study drug infusion. (See protocol for definition of **life-threatening hypotension** and **life-threatening cardiac arrhythmia**).

Other Safety Outcomes:

- Life-threatening hypotension
- Life-threatening cardiac arrhythmia
- Mortality
- Need for endotracheal intubation
- Acute recurrent seizure
- Acute anaphylaxis
- Respiratory depression
- Hepatic transaminase or ammonia elevations
- Purple glove syndrome

Each Closed DSMB report will test for differences in safety events in treatment groups using a chi-squared test or Fisher's exact test. Safety events will also be reported by weight group (< 75kg or $\geq$75 kg). Since there are multiple comparisons and multiple looks, the pre-specified level of significance is 0.01.

15.3 ANALYSIS OF SECONDARY OUTCOMES

At the final analysis, the secondary outcomes will be compared by treatment group. All secondary outcomes will be tested at a significance level of two-sided alpha of 0.05. Binary outcomes will be compared by first testing the null hypothesis that the proportion of responses for all three treatment groups are equal in a χ^2 test (or Fisher's exact test depending on frequency of events). If the three-way null hypothesis is rejected, then all pairwise comparisons will be performed as two-sample tests of proportions. Continuous outcomes will be compared in an F-test (or Kruskal-Wallis test if normality assumption is violated) to test the null hypothesis that all three treatment groups are equal, followed by pairwise t-tests (or Wilcoxon Rank sum test). The Richmond agitation and sedation score (RASS) at 60 minutes will be compared by treatment groups in a Kruskal-Wallis test. The secondary outcomes will also be compared by treatment group within age group. Kaplan Meier curves and log rank tests will be used to compare time to event outcomes by treatment group. Since mortality is expected to increase by age, a cox proportional hazard model will be used to estimate the hazard ratio and 95% CI for the treatment groups adjusting for age groups and age by treatment interaction terms. If the assumptions for the cox proportional hazard model are not met, Kaplan Meier curves and log rank tests will be used to compare time to mortality by treatment group within each age group.

15.4 SAFETY MONITORING

Active monitoring for all adverse events (AEs) will occur throughout the study by the Data Safety Monitoring Board (DSMB) and as further described in the Safety Monitoring Plan.

16 SCENARIOS

16.1 ANALYSIS SAMPLES

SCENARIO	ITT SAMPLE	Per Protocol SAMPLE	Re-Enroller SAMPLE
Infusion pump/Catheter turned on	X	X	X
Infusion was stopped after 2 minutes (patient received less than 80% of study drug)	X		X
Patient did not met eligibility criteria	X		X
Patient was 20 years old, but received the pediatric use next box (e.g. age estimated incorrectly or the adult use next box was missing).	X*	X*	X*
Patient was previously enrolled	**	**	X

*In the analysis, the patient is classified in actual/true age strata and classified in the treatment group they actually received.

**Only the first enrollment is included in the analysis.

16.2 TARGET RANDOMIZATION UPDATES

The target randomization probabilities will be updated based on the primary efficacy outcome (section 4) using the methodology described under section 6.

The trial operating characteristics (power and type I error rate) are dependent on carefully following the pre-specified timing of randomization updates and the early stopping rules. Unlike some trials in which there is leeway in the number and timing of interim looks, this design is planned to have fixed adaptations. Prior to implementing the updated allocation probabilities, the DSMB/DSMB Chair will be asked to review and approve them.

Example of Updated Allocation Probabilities after 300 patients are enrolled:

	N Enrolled								
	Observed Response Rate (Primary Outcome)			**Probability that a treatment is the most effective**			**Updated Randomization Probabilities (r_t)**		
Look	**FOS**	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**	**FOS**	**LVT**	**VPA**
	51/99	55/100	64/101						
300	52%	55%	63%	0.025	0.092	0.88	0.12	0.22	0.66

1 REFERENCES

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2 APPENDIX

DESIGN DOCUMENT FROM BERRY CONSULTANTS

Berry Consultants
Statistical Innovation

Adaptive Trial Design for the Established Status Epilepticus Treatment Trial (ESETT)

By Berry Consultants, LLC
August 22, 2013

1.0 Background

This is a Phase III comparative effectiveness trial in patients with established status epilepticus who have failed benzodiazepines. The primary objective is to determine the most effective and/or the least effective treatment. The primary efficacy outcome for the study is clinical cessation of status epilepticus sustained for 60 minutes from the start of study drug infusion, without further intervention with anti-seizure or sedative medications. . There are three active treatment arms, fosphenytoin (fPHT), levetiracetam (LVT), and valproic acid (VPA). Adaptive randomization will be used to allocate patients to the three treatment arms. This trial will be monitored for early success and futility. The ESETT trial plans to enroll a maximum of 795 patients. However, the operating characteristics reported in this document were determined assuming a maximum sample size of 720 (uninflated for re-enrollers, missing data, and protocol violations).

2.0 Statistical Modeling

2.1 Primary Endpoint

Each of the three treatment arms is modeled independently. We assume the probability of success, θ_T, has a Beta prior distribution

$$[\theta_T] \sim \text{Beta}(1,1)$$

for $T \in$ {fPHT, LVT, VPA}.

This prior distribution is equivalent to observing two patients' worth of information where one experienced a success and one did not. At each interim analysis the number of observed successes on each treatment, X_T, among the currently enrolled patients on treatment T, N_T, follows a binomial distribution

$$[X_T] \sim \text{Binomial}(N_T, \theta_T).$$

We update the prior distribution with the currently observed data for each treatment arm (X_T, N_T) and the resulting posterior distribution on each arm is

$$[\theta_T | X_T, N_T] \sim \text{Beta}(1+X_T, 1+N_T-X_T).$$

From each posterior we will also calculate the probability that each treatment offers the best and worst treatment effect. The treatment offering the best treatment effect is labeled t_{max} while the treatment offering the worst treatment effect is labeled t_{min}. Of course during the trial it will not be know which treatment is t_{max} and which is t_{max}, however we can apply probabilities that each of the three treatments is t_{max} and t_{min}.

The probability treatment T is the best treatment, $\Pr(T = t_{max}) = \Pr(\theta_T > \theta_X \text{ and } \theta_T > \theta_Y)$ where X and Y represent the two treatments other than treatment T. Likewise, the probability treatment T is the least effective treatment, $\Pr(T = t_{min}) = \Pr(\theta_T < \theta_X \text{ and } \theta_T < \theta_Y)$ where X and Y represent the two treatments that are not treatment T.

This model will be used at each interim analysis and the final analysis.

2.2 Primary Efficacy Analysis

At the conclusion of the trial, we will report the response rates for each treatment group with 95% credible intervals as well as the pairwise differences in response rates with 95% credible intervals.

In addition, we will calculate and report the posterior probabilities that each treatment, T, is the most and least effective treatment, $\Pr(T=t_{max})$ and $\Pr(T=t_{min})$. This trial will be considered a success if $\Pr(T=t_{max}) > 0.975$ and/or $\Pr(T'=t_{min}) > 0.975$ for any treatments T and T'. This represents that the trial has identified the best or worst treatment with high probability.

3.0 Possible Adaptations

Interim analysis will occur after 300, 400, 500, 600 and 700 patients are enrolled (assuming the trial has not stopped before such time points).

At each interim analysis there may be updates to the randomization probabilities (at or beyond 300 patients) and/or the trial may stop early for success (at or beyond 400 patients) or futility (at or beyond 400 patients).

3.1 Adaptive Allocation

The initial 300 patients will be randomized equally to the three treatment arms. Thus, 100 patients will be allocated to each arm. After the initial 300 patients, adaptive randomization will begin. Adaptive randomization will focus on identifying the treatment arm offering the highest response rate, labeled t_{max}, by using information weighting. It is unknown during the trial which arm is truly t_{max}, the treatment offering the highest true response rate. Therefore, throughout the trial we assign probabilities, based on the ever-accumulating data, that each treatment is t_{max}.

We use this measure, along with the information on each arm to update randomization probabilities using information-weighted adaptive randomization. Information is a measure of the expected reduction in variance from adding an additional patient and is defined for treatment arm, *T*, as

$$I_T = \sqrt{\frac{\Pr\left(T = t_{\max}\right) Var\left(\theta_T\right)}{n_T + 1}}$$

where Pr(T=t_{max}) is the probability that treatment t is the maximum effective treatment t_{max}, Var(θ_T) is the posterior variance of the response rate, and n_T is the current number of patients allocated to treatment T. Once I_T is calculated for all three treatment arms, the values are rescaled so the probabilities sum to 1. Therefore the randomization probability, r_T, to treatment T is

$$r_T = \frac{I_T}{\sum_{t=1}^{3} I_t}.$$

If the adaptive randomization probability for an arm is less than 5%, this probability is set to zero and the remaining arms receive proportionally increased probability. In this manner, arms are effectively dropped, but may be re-introduced if the adaptive randomization probability increases at subsequent interim analyses. Adaptive randomization probabilities will be updated starting when 300 patients are enrolled and after every additional 100 patients are enrolled.

Allocation to the treatment arms will be stratified by age group (2-16 years, 16-65 years, and greater than 65 years). We will use a "Step Forward" randomization procedure, as described in Zhao et al (2010). This algorithm requires a target randomization proportion for each treatment arm. This target proportion will be equal allocation for the first 300 patients (1/3 to each arm) and will be updated according to the adaptive allocation probabilities when 300 patients have been enrolled and after every additional 100 patients have been enrolled.

3.2 Interim Monitoring for Success

Interim monitoring for success will begin after 400 patients have been enrolled and will be repeated after every additional 100 patients are enrolled. Interim monitoring is based on the treatment identified as the maximum effective treatment (t_{max}). This trial will stop early for success if we have identified the maximum effective treatment with at least 97.5% probability, that is if any arm $T \in$ {fPHT, LVT, VPA} offers

$$\Pr(T = t_{max}) \geq 0.975.$$

3.4 Interim Monitoring for Futility

Interim monitoring for futility will begin after 400 patients have been enrolled and will be repeated after every additional 100 patients are enrolled. There are two early futility criteria. The first futility rule will stop the trial early if all treatment arms have clinically unacceptable success rates. The second futility rule will stop the trial early if all treatments are performing similarly and we will be unable to identify a most effective or least effective treatment.

First, any treatment arm will be terminally dropped if its response rate is clearly less than 25%:

$$\Pr(\theta_T \geq 25\%) < 0.05.$$

Therefore the trial will stop early if there is a low probability that any of the three treatment arms is achieving a success rate of at least 25%. If all three of the following conditions are met, the trial stops for futility:

$$\Pr(\theta_{fPHT} \geq 25\%) < 0.05$$
$$\Pr(\theta_{LVT} \geq 25\%) < 0.05$$
$$\Pr(\theta_{VPA} \geq 25\%) < 0.05.$$

The second futility stopping criteria applies if the trial is unlikely to achieve its primary objective, to identify the most effective and/or the least effective treatment. This trial will stop early for futility if the predictive probability of identifying either the most effective (t_{max}) or the least effective treatment (t_{min}) is less than 5%.

This calculation proceeds as follows.

1. For an interim analysis at N patients we have posterior probability distributions for each treatment arm as described in Section 2.0.
2. Assuming that the randomization for the rest of 720 – N patients will proceed with the current randomization probabilities, the number of patients to be randomized to each of the three treatment groups is $M_T = r_T$ (720 – N).
3. The number of predicted successes, s_T on each arm therefore has a Beta-Binomial distribution $s_T \sim$ Beta-binomial(M_T, $1+X_T$, $1+N_T-X_T$). So every possible resulting number of successes on each arm, $X_T+S_T = X_T, X_T+1,\ldots, X_T+M_T$ is assigned a probability.
4. There $(M_{fPHT}+1) \times (M_{LVT}+1) \times (M_{VPA}+1)$ possible trial outcomes. For each possible set of final trial data, $X_{fPHT}+S_{fPHT}$ / $N_{fPHT}+M_{fPHT}$, $X_{LVT}+S_{LVT}$ / $N_{LVT}+M_{LVT}$, $X_{VPA}+S_{VPA}$ / $N_{VPA}+M_{VPA}$, we calculate the probability of each observed triplet and whether that result, using the methods in Section 2.2, would result in identifying a best or worst treatment with 97.5% probability.

5. We sum the probabilities for which a best and/or worst treatment would be identified. This sum represents the predicted probability of trial success at the maximum sample size. If this sum is < 5%, the trial stops for futility. This case would occur when all three treatment are performing very similarly and it is unlikely that acquiring further data would identify a best or worst treatment.

4.0 Example Trials

The tables below show two example trials in order to better understand the adaptive trial.

Example 1

First we see a trial that stops early for success after 600 patients are enrolled. At the first interim analysis when 300 patients are enrolled we see success rates of 51% for fPHT, 55% for LVT and 64% for VPA. At this interim analysis there is a 88% chance VPA offers the best treatment effect and a 70% chance fPHT offers the worst treatment effect. The randomization probabilities for the next 100 patients are calculated to be 12%, 22% and 66% to fPHT, LVT, and VPA, respectively.

	Observed Successes / Randomized			Probability Best Trt Probability Worst Trt			Randomization Probs for Next 100 Pts			Pred Prob
N	fPHT	LVT	VPA	fPHT	LVT	VPA	fPHT	LVT	VPA	
300	51/100 51%	55/100 55%	64/100 64%	0.025 0.70	0.092 0.29	0.88 0.014	0.12	0.22	0.66	0.71
New	6/11 55%	19/26 73%	39/63 62%							
400	57/111 51%	74/126 59%	105/163 64%	0.010 0.87	0.16 0.13	0.83 0.008	0.094	0.34	0.57	0.50
New	5/12 42%	20/38 53%	34/50 68%							
500	62/123 50%	94/164 57%	139/213 65%	0.004 0.88	0.056 0.12	0.94 0.002	0.080	0.23	0.69	0.59
New	3/3 50%	17/28 57%	55/69 65%							
600	65/126 52%	111/192 58%	194/282 69%	0.000 0.87	0.008 0.13	0.992 0.00	--	--	--	---

We in fact see 11, 26, and 63 patients randomized to fPHT, LVT, and VPA, respectively and LVT having the highest success rate with 19/26 (73%) of the new patients randomized to it being successes. So at the 400-patient analysis we see success rates of 51%, 59%, and 64%, fPHT, LVT, and VPA, respectively. The observed benefit of VPA over LVT decreases from 64% vs. 55% at the first analysis to 64% vs. 59% now, however this smaller benefit it is based on more data. The probability that VPA is the best treatment (offering the highest response rate) decreases slightly from 88% to 83%. We also see a higher randomization

probability to LVT in the next set of patients. The predictive probability of trial success (the probability of identifying a best or worst treatment at the maximum sample size) is 0.50, well about the 5% threshold to stop for futility. Therefore the trial continues with another interim analysis after 500 patients are enrolled.

VPA again had the best response rate in the next 100 patients (68% vs. 42% for fPHT and 53% for LVT). The probability that VPA offers the best treatment effect is 94%, high but not exceeding the 97.5% we need to stop the trial early for success.

Therefore we enroll another 100 patients, 69% to VPA, 23% to LVT, and 8% to fPHT. At the 600-patient analysis after these patients are enrolled we see that VPA has a 99.2% chance of offering the best treatment effect. As this exceeds 97.5% the trial is stopped early and the results reported with VPA offering the superior response rate. At that time we also see fPHT has an 87% chance of having the lowest response rate.

Final summaries will also include 95% confidence intervals for the response rates on each arm and for the pairwise differences.

Example 2

Example 2 illustrates a case where the trial stops early for futility.

After the 300-patient analysis fPHT is looking better with a response rate of 54% vs. 48% for LVT and just 42% for VPA. The predictive probability calculation shows a 48% chance that this trial will identify either a best or worst treatment, though the trial could not stop at 300 patients.

	Observed Successes / Randomized			Probability Best Trt Probability Worst Trt			Randomization Probs for Next 100 Pts			Pred Prob
N	fPHT	LVT	VPA	fPHT	LVT	VPA	fPHT	LVT	VPA	
300	54/100 54%	48/100 48%	42/100 42%	0.79 0.027	0.19 0.20	0.025 0.78	0.60	0.29	0.11	0.48
New	25/55 45%	15/36 42%	4/9 44%							
400	79/155 51%	63/136 46%	46/109 42%	0.74 0.044	0.20 0.24	0.06 0.72	0.50	0.30	0.20	0.22
New	21/51 41%	12/25 48%	18/24 75%							
500	100/206 49%	75/161 47%	64/133 48%	0.40 0.23	0.22 0.47	0.38 0.30	--	--	--	0.02

The trial continues and the majority of the next 100 patients are randomized to fPHT but the response rates in the next 100 patients are very similar (45% vs. 42% vs. 44%). Therefore the updated response rates see fewer fewer (50%) of patients going to fPHT, 30% to LVT, and 20% to VPA. After these 100 patients (which sees

fPHT have the lowest respose rate) the overall response rates are very similar across groups: 49% for fPHT, 48% for VPA, and 47% for LVT. The rates are so similar, the predictive probability calculation shows that if another 220 patients are enrolled to achieve the 720 patient maximum, there is just a 2% chance that the trial will identify either a best or worst treatment. Since this probability of achieving the trial's primary aim is less than 5%, the trial stops for futility.

5.0 Operating Characteristics

To evaluate how the design performs, we simulated the trial considering different success rate scenarios. Operating characteristics are based on 100,000 simulations per scenario. Table 1 shows the success rate scenarios.

Table 1: Success Rate Scenarios

	fPHT	LVT	VPA
a) Null	50%	50%	50%
b) One Good	50%	50%	65%
c) Two Good	50%	65%	65%
d) One Middle One Good	50%	57.5%	65%
e) All Bad	25%	25%	25%
f) All Really Bad	10%	10%	10%

These six scenarios represent a range of effects including three cases where all drugs are equally efficacious (a,e,f), a case where one is far superior to the other two (b), another where one is far inferior to the other two (c), and another where the effect sizes are spread out (d). The bottom two cases illustrate scenarios where none of the three drugs' benefits exceed the minimum efficacy requirement.

Table 2 shows the probabilities of trial success for each of the 6 success rate scenarios. We show 1) the probability of stopping the trial early for success, defined by identifying the t_{max} with greater than 97.5% probability below the maximum sample size; 2) the probability of continuing the trial to the maximum sample size and declaring success by identifying the t_{max} with greater than 97.5% probability; 3) the overall probability of identifying the t_{max} with > 97.5% probability (early or at the maximum sample size); 4) the overall probability of identifying t_{min} with > 97.5% probability (early or at the maximum sample size); and 5) the probability of trial success by identifying t_{max}, t_{min}, or both with > 97.5% probability.

The false positive rate of this trial is the probability of identifying either the most or the least effective treatment, when in truth there is no difference between the arms. This is illustrated in the "Null" scenario where all treatment arms have the same success rate. In this scenario, the probability of identifying a maximum effective treatment is 0.017 and the probability of identifying a least effective treatment is 0.021. Thus, the false positive rate in this scenario is 0.038, less than a standard 0.05 level. Similarly, in the "All Bad" and "All Really Bad" scenarios the false positive

rate is 0.036 and 0.005 respectively. In the "Two Good" scenario, two of the treatment arms have the same success rate and the probability of identifying one of these as the t_{max} is 0.11. Similarly, in the "One Good" scenario, the false positive rate is 0.039 of erroneously identifying of the two equally poor treatments as the worst.

Table 2: Probabilities of Trial Success

Scenario	Pr identify t_{max} Early	Pr identify t_{max} at maximum SS	Prob identify t_{max}	Prob identify t_{least}	Pr Success (identify t_{max} or t_{least})
Null	0.016	0.001	0.017	0.021	0.037
One Good	0.888	0.011	0.899	0.039	0.908
Two Good	0.101	0.005	0.106	0.685	0.765
One Middle One Good	0.473	0.019	0.492	0.235	0.676
All Bad	0.016	0.001	0.016	0.020	0.036
All Really Bad	0.005	0.000	0.005	0.000	0.005

Alternatively, the true positive rate of this trial is the probability of identifying either the most or the least effective treatment when there are differences in the success rates. In the "One Good" scenario, one treatment arm has a 65% success rate compared to a 50% success rate in the other two arms. The probability of identifying a maximum effective treatment is 90%. In the "Two Good" scenario, one arm is ineffective (50% success rate) relative to the other two (65% success rate) and the probability of identifying a least effective treatment is 69%. In the "One Middle One Good" scenario, there is a modest treatment effect in one arm and a strong treatment effect in another arm. The probability of identifying the best arm as the best is 49%; the probability of identifying either a maximum or a least effective treatment is 68%.

Table 3 shows the mean sample size and the mean allocation to each of the three treatment arms for each of the success rate scenarios. The proportion of the total sample size allocated to each arm is shown in parentheses. The most effective treatment arm(s) is shown in bold-italics. Adaptive allocation tends to place a higher proportion of patients on the most effective treatment arm(s).

Table 3: Mean Allocation (Proportion of Total Mean Allocation)

	Total	fPHT	LEV	VPA
a) Null	508	169 (33%)	169 (33%)	169 (33%)
b) One Good	484	127 (26%)	127 (26%)	***231 (47%)***
c) Two Good	684	115 (17%)	***284 (41%)***	***284 (41%)***
d) One Middle One Good	592	123 (22%)	190 (32%)	***279 (47%)***
e) All Bad	522	174 (33%)	174 (33%)	174 (34%)
f) All Really Bad	400	133 (33%)	133 (33%)	133 (34%)

For example in the One Good and One Middle, One Good scenarios, 47% of patients are randomized to the best treatment, compared to 33% that would be in a trial with fixed randomization. In the scenario where one treatment is worse than the two other equally good treatments, just 17% of patients are randomized to the inferior treatment vs. 33% in a trial with fixed randomization. In the scenarios where there is no difference between treatment arms (Null, All Bad, All Really Bad) patients are, on average, evenly allocated.

In every trial one arm will be identified as the t_{max}, however, the probability the best observed arm is the t_{max} may not exceed 97.5%, the criteria to successfully claim we have identified the t_{max}. Table 4 shows the probability each arm is identified as the maximum effective treatment (t_{max}) and the probability each arm is identified as the maximum effective treatment with at least 97.5% probability (i.e. obtains the success criteria). The arm(s) with the highest true success rate is shown in bold-italics. In the "One Good" scenario, the arm with the highest success rate is identified as the t_{max} with 99.6% probability and this arm will achieve the success criteria with 90% probability. In the "Two Good" scenario, two arms have the same success rate. Thus, the probability of being t_{max} is split between these two arms and each receives approximately 50% probability of being t_{max}. In the "One Middle One Good" scenario, the arm with the highest success rate is identified as the t_{max} with 96% probability and this arm will achieve the success criteria with 49% probability.

Table 4: Probability of declaring $t=t_{max}$

	Proportion t_{max}			Proportion Pr(t_{max}) > 0.975		
Scenario	**fPHT**	**LEV**	**VPA**	**fPHT**	**LEV**	**VPA**
a) Null	0.33	0.33	0.34	0.005	0.006	0.006
b) One Good	0.002	0.002	***0.996***	0.00	0.00	***0.90***
c) Two Good	0.001	***0.50***	***0.50***	0.00	***0.05***	***0.05***
d) One Middle One Good	0.002	0.04	***0.96***	0.00	0.00	***0.49***
e) All Bad	0.33	0.34	0.33	0.005	0.005	0.005
f) All Really Bad	0.34	0.33	0.33	0.002	0.002	0.001

Operating characteristics were calculated from 100,000 simulated trials for each of the six scenarios. Therefore even when two treatments have the same efficacy, some operating characteristic values aren't precisely equal.

Table 5 compares the Bayesian adaptive design to a similar design with early stopping but not adaptive randomization.

In scenarios where one drug offers a superior outcome rate to the other two drugs, adaptive randomization increases the power to identify the best treatment (90% vs. 87% in the One Good scenario; 49% vs. 45% in the One Middle, One Good scenario) while requiring a slightly lower expected sample size (484 vs. 492 in the One Good scenario; 592 vs. 597 in the One Middle, One Good Scenario) and randomize a higher proportion of patients to the best therapy (47% vs. 33% in the One Good scenario; 47% vs. 33% in the One Middle One Good scenario).

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Table 5: Effect of Adaptive Randomization

	Adaptive Randomization			Fixed Randomization		
Scenario	**Power**	**Mean N**	**% to Best**	**Power**	**Mean N**	**% to Best**
a) Null 0.50 – 0.50 – 0.50	0.037 0.017 – 0.021	508	N/A	0.031 0.023 – 0.009	499	N/A
b) One Good 0.50 – 0.50 – 0.65	0.91 0.90 – 0.04	484	47	0.88 0.87 – 0.04	492	33
c) Two Good 0.50 – 0.65 – 0.65	0.77 0.11 – 0.69	684	83	0.86 0.10- 0.80	686	67
d) One Middle One Good 0.50 – 0.575 – 0.65	0.68 0.49 – 0.24	592	47	0.70 0.45 – 0.31	597	33
e) All Bad 0.25 – 0.25 – 0.25	0.036 0.016– 0.020	522	N/A	0.029 0.021 – 0.009	507	N/A
f) All Really Bad 0.10 – 0.10 – 0.10	0.005 0.005 – 0.000	400	N/A	0.007 0.007 – 0.00	400	N/A

% to Best = Average proportion of patients randomized to the most effective therapy.
Values under Power are probability of identify a best and/or worst drug (top row), best drug (bottom left), and worst drug (bottom left).

When the treatments are truly equally effective, Type I error rates remain well controlled and the expected sample sizes are slightly higher.

6.0 Summary

This novel Bayesian adaptive comparative effectiveness trial uses adaptive randomization with early stopping to create an efficient trial that offers (1) a smaller expected sample size, (2) higher power, and (3) a higher proportion patients are likely to be randomized to the best treatment arm when one treatment is superior to the other two.

This comparative effectiveness design was presented at the Agency for Healthcare Research and Quality 2012 conference "Methods for Comparative Effectiveness Research/Patient-Centered Outcomes Research: From Efficacy to Effectiveness" and published (Connor, Elm, & Broglio) in the associated special issue of the *Journal Clinical Epidemiology* August 2013. In that issue's introductory remarks, the conference organizers, Sebastian Schneeweiss, John Seeger, John Jackson, and Scott Smith, claim "The paper by Connor et al. on Bayesian Adaptive Trials for CER makes a strong case for the usefulness of adaptive trial designs for more efficiently using study resources, maximizing patient benefit and minimizing patient risk in CER." (*J. Clin Epi.*, August 2013 page S3).

7.0 References

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