

## SYNOPSIS

The Established Status Epilepticus Treatment Trial (ESETT): A multicenter, randomized, double-blind, comparative effectiveness study of fos-phenytoin (FOS), levetiracetam (LEV), and valproic acid (VPA) in subjects with benzodiazepine-refractory status epilepticus (SE).

**Objectives:** The **primary** objective is to determine the most effective and/or the least effective treatment of benzodiazepine-refractory 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. Final objective is to ensure that the trial is informative for treatment of ESE in children by describing the effectiveness, rate of adverse reactions of these drugs in children.

**Primary outcome** is clinical cessation of status epilepticus, without recurrent seizures, or use of additional anti-seizure medications within 60 minutes of the start of study drug infusion. Clinical cessation of SE consists of absence of clinical seizures and improving responsiveness. The following **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, and mortality, Richmond agitation and sedation score at primary outcome determination, 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 benzodiazepines. Each subject will be followed until discharge or 30 days from enrollment. This trial will be monitored for early success and futility.

**Inclusion:** Patients older than 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: diazepam 10 mg IV, lorazepam 4 mg IV, or midazolam 10mg IV or IM for subjects above 40 kg, and diazepam 0.3mg/kg IV, lorazepam 0.1 mg/kg IV or midazolam 0.3mg/kg IV or IM for subjects between 10-40 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). These drugs, along with an Itouch study device and tubing, will be placed in study boxes kept in ED drug refrigerator. The assigned treatment dose (FOS 20 mg/Kg, LEV 60 mg/Kg or VPA 40 mg/Kg) will be infused over 10 minutes. The patients will be observed for 20 minutes, when the duration of clinical seizures and response to verbal or painful stimuli will be recorded. At 60 minutes from enrollment, a study team member will determine the primary outcome.

**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 emergent and life-threatening nature of SE. This is an intention to treat study. Enrollment occurs when the infusion pump connected to study drug vial and patient's IV catheter is switched on and the time of enrollment recorded on the study device. 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. Throughout the trial, randomization will be stratified by three age groups (2-18 years, 19-65 years, and 66 years and older).

**Interim Analyses:** 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. This trial will stop early for success if we have identified the maximum effective treatment with at least 97.5% probability.

**Sample Size:** 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. This sample size 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%). 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.<sup>37</sup>

**Participating Sites:** Patients will be recruited by two national emergency research networks: Neurology Emergency Treatment Trials network (NETT) and Pediatric Emergency Care and Applied Research Network (PECARN). Each network has successfully undertaken a SE treatment trial under EFIC rules.