Intramuscular midazolam versus intravenous lorazepam in the pre-hospital treatment of status epilepticus (the RAMPART trial) Project Summary

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**Target disease: Status Epilepticus (SE).**
Status epilepticus is a true neurologic emergency associated with significant morbidity and mortality. It has been estimated that there are between 120,000 and 200,000 cases of status epilepticus in this country each year resulting in as many as 55,000 deaths. An incidence of between 6.2 and 18.3 per 100,000 persons has been reported in the United States. 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.

**Primary objective:** To determine the effectiveness and rapidity of intramuscular (IM) midazolam versus intravenous (IV) lorazepam in the pre-hospital treatment of status epilepticus. Effectiveness will be assessed by the proportion of subjects with termination of clinically evident seizure determined at arrival in the Emergency Department (ED) after a single dose of study medication. Rapidity will be determined by comparing intervals from paramedic arrival and initiation of treatment to the termination of clinically evident seizure.

**Secondary objectives:** To examine the effects of IM midazolam versus IV lorazepam on neurologic outcome at 90 days, frequency of endotracheal intubation, the frequency and duration of ICU admission, and the frequency and duration of pharmacologic coma. Markers of safety include the frequency of seizure recurrence and oversedation related to anticonvulsant therapy.

**Scientific rationale:** Background
Seizures are a common cause of emergency medical services (EMS) activation. Although seizures arise from many etiologies, prolonged seizure activity from any cause is a dangerous neurologic emergency in both adults and children. Traditionally status epilepticus (SE) has been defined as seizure activity persisting for greater than 30 minutes or lack of return to baseline function between seizures within a 30 minute interval, but more recently it has been suggested that duration of even 5 minutes or more is deleterious and should be considered indicative of status. The importance of rapid termination of seizures is not surprising. In both humans and experimental animals, the duration of sustained seizure activity is closely related to extent of neuronal injury. Even in the absence of hemodynamic compromise or hypoxia, status epilepticus is associated with excitotoxic and apoptotic cell death. Optimal outcomes in patients with refractory status epilepticus is therefore likely to depend on treatments that lead to rapid cessation of seizure.

In the pre-hospital setting, the use of intravenous (IV) lorazepam has been shown to effectively terminate seizures in patients with status epilepticus, and therefore reduce the incidence of status upon arrival in the emergency department (ED). However, several factors limit the utility of intravenous lorazepam in the pre-hospital setting. First, the need to establish intravenous access can be problematic. Starting an IV can be difficult or time consuming in patients with convulsive limb activity. The risk of accidental needle stick injury to health care personnel also increases when patients are seizing. In many pre-hospital settings, such as in patients with known refractory seizures, or in mass causality environments, it would be advantageous to have a route of delivery that did not require personnel skilled at starting IV’s. Second, lorazepam is not an ideal drug for most EMS systems or for disaster preparedness efforts because under typical non-refrigerated storage conditions, the drug breaks down and should be restocked every 90 days. Also, lorazepam, like diazepam, is relatively poorly absorbed when given intramuscularly (IM) or across mucus membranes compared to more lipophilic benzodiazepines.

Ideally, the optimal pre-hospital therapy for status epilepticus may be a benzodiazepine given intramuscularly immediately upon EMS arrival at the scene of a patient with ongoing seizure activity. Midazolam is highly lipophilic agent that is rapidly absorbed intramuscularly with subsequent very rapid distribution in the CNS. Midazolam has been shown to be highly effective at terminating seizures both when given as an initial agent for status epilepticus and when given as second line therapy for refractory SE. Midazolam has not been studied in a randomized controlled manner for the termination of seizures in children and adults in the pre-hospital setting.

Rapid termination of seizures is therapeutic. 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. Recent literature suggests that the clinically useful definition of status epilepticus is as continuous or repeated seizure activity for more than five minutes without recovery of consciousness. Clinical data have demonstrated the duration of SE is associated with death and unfavorable neurologic outcomes. 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.

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. 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.

Midazolam by non-intravenous routes speeds termination of seizures. Benzodiazepines are an effective first line pharmacotherapy for acute SE, but the need to establish vascular access to administer these drugs intravenously is a barrier to rapid treatment in the pre-hospital or emergency environment. Paramedics are adept at securing such access, but doing so in patients with SE has several potential difficulties. Patients with SE are often children. Access is often more difficult in children and paramedics are often less experienced at starting IVs in children. Furthermore, tonic clonic limb activity makes starting an IV more difficult and increases the likelihood of needlestick injury to the health care worker.

Non-intravenous routes of administration of midazolam, intramuscular and intranasal, have been
proposed for emergent treatment of patients with SE in order to circumvent these difficulties and speed initiation of therapy. When studied, the time saved by not having to secure venous access prior to treatment has been shown to be greater than the difference in onset of action between IV and non-IV administration.

We performed a systematic review and identified four randomized controlled trials \(^{15-18}\) and one observational study \(^{6}\) that compared midazolam given by IM or IN routes with intravenous diazepam in the emergency setting, either in the ED or in the field. The efficacy of IM/IN midazolam versus IV diazepam with regard to proportion of patients with termination of seizure and mean time from initiation of treatment to termination of seizure are shown in Figure 1 using Cochrane meta-analytic methodology. This analysis demonstrates that non-intravenous midazolam and IV diazepam have similar efficacy at terminating seizures, but IM/IN midazolam is consistently quicker at terminating seizures with fixed weighted mean difference of about 3 minutes.

The source trials in this meta-analysis confirmed the safety of non-intravenous midazolam as compared to diazepam. In the four randomized controlled trials no episodes of respiratory depression or hemodynamic instability were noted in any group. In the observational pre-hospital study and another observational study comparing IM to IV midazolam, IM midazolam was not associated with any respiratory or other complications. \(^{6, 7, 15-18}\)

Additional clinical trial data are needed to address several limitations of this meta-analysis. These include problems with the external validity of the analysis on other patient populations. The source trials of this analysis were exclusively pediatric and most were based in the ED. Also these source studies compared midazolam to diazepam, while lorazepam has increasingly become used as the standard initial treatment for seizures. A clinical trial comparing IV lorazepam to IM midazolam in children and adults in the pre-hospital environment would address these limitations.

Favorable pharmacology of IM midazolam. There is a well documented pharmacologic basis underlying the favorable clinical trial experience with IM midazolam in the emergency treatment of seizures. The pharmacokinetics of IM midazolam is summarized from several sources in Table 1 which shows the mean and reported range of parameters. Importantly, midazolam is rapidly and extensively absorbed from the intramuscular space with a lag time to appearance in the serum of less than 2

<table>
<thead>
<tr>
<th>Table 1. Midazolam pharmacokinetics summary</th>
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<tr>
<td>Parameter</td>
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<td>T(\text{max})</td>
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<td>T(1/2)</td>
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<tr>
<td>AUC</td>
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<tr>
<td>V(\text{dss})</td>
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<td>CL(\text{e})</td>
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From IM doses of 0.08-0.15 mg/kg. Refs 19-23

Midazolam has some unusual kinetics. Its half life of elimination is 2.5 hours on average, which is shorter than other benzodiazepines used to treat SE, but unlike these other benzodiazepines, brain concentrations of midazolam remain relatively high even as serum levels are cleared. As seen in

Figure 2. (from Alfonzo-Echeverri 1990) demonstrates that serum concentrations are near 80% of peak as early as 5 minutes after IM admin.

Figure 3. (from Megarbane 2005) demonstrates that brain concentration remains high even as serum concentration is dropping.
Figure 3, brain concentrations of midazolam measured by microdialysis remain within 25% of peak levels more than 4 hours after IM administration.\textsuperscript{24}

The pharmacodynamics of IM midazolam in the treatment of seizures follows from the kinetics. IM midazolam controls experimental seizures more rapidly than diazepam, and suppresses ictal spikes for a longer time, despite its relatively quick serum clearance.\textsuperscript{25} Clinical experience also supports the finding that midazolam does not have a higher rate of recurrent seizures as compared to other benzodiazepines.\textsuperscript{16, 18}

Current EMS practice. Pre-hospital care of the patient with status epilepticus in the US is somewhat variable. In the past, EMS systems had provided only supportive care and rapid transport to patients with ongoing seizures. Currently, most paramedic systems provide treatment of status epilepticus with IV or rectal diazepam to attempt to terminate convulsions.\textsuperscript{6} Depending on the system, treatment may be given by protocols with standing orders or with direct medical oversight by communication with a local base hospital ED. We demonstrated the benefits of paramedic initiated therapy with benzodiazepines in the Pre-hospital Treatment of Status Epilepticus (PHTSE) Trial conducted by Dr. Lowenstein and colleagues.\textsuperscript{26} PHTSE was an NINDS funded randomized controlled trial of diazepam, lorazepam, and placebo in the pre-hospital treatment of SE. While both diazepam and lorazepam were more effective than placebo in PHTSE, the trial suggested that IV lorazepam may be more effective than IV diazepam.\textsuperscript{3} Adoption of IV lorazepam has been slow because of limitations inherent to storage and stocking of the medication in EMS environments. The use of midazolam by paramedics for treatment of SE in the field has been reported but is currently exceedingly rare.\textsuperscript{6, 7}

Design and intent of study. This is a double-blind randomized clinical trial of the efficacy of IM midazolam versus IV lorazepam in the pre-hospital treatment of status epilepticus by paramedics. It is called the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART).

Intervention. Paramedic units are provided and trained in the use of kits containing study medication and a custom data logging device (RMV electronics, Vancouver BC). Medications are stored in sealed opaque study plastic boxes which are supplied to EMS crews in a randomized manner. Each box contains two syringes. One syringe has a hypodermic needle (21 gauge 1.25 inch) attached, and the other has an intravenous line connector tip (compatible with each EMS systems needle-less system) attached. In each kit one of the two syringes is filled with study medication, and the other with saline placebo. When the study medication is in the syringe with the needle, the study medication is midazolam 10 mg. When the study medication is in the syringe with the IV tip, the study medication is lorazepam 4 mg. Study medications and placebo are all prepared in a volume of 4 mL. Adults and children over 50 kg are treated with the full dose provided in each syringe. Children that may be less than 50 kg are treated with weight adjusted doses, IM midazolam 0.2 mg/kg or IV lorazepam 0.1 mg/kg. Dosing is based on an estimated weight based on subject height/length. A Broselow tape\textsuperscript{27} modified for this study and included in each kit shows the dose in mL to be given for each route of administration for pediatric subjects. Kits are distributed to EMS crews by block randomization. Subjects are allocated to treatment group by the kit carried by the EMS crew.

A small custom data logger is built into each study box containing a global positioning system (GPS) receiver, temperature sensor, and voice recorder. Boxes are distributed to EMS crews and exchanged after any use or after 60 days. The logger records temperature and location continuously during that period. A switch inside the box is activated by opening the box to access the medications. The GPS unit determines time of EMS arrival by logging the time the box arrived within 100 feet of the location where it was opened. The voice recorder is also activated by opening the box. The box is secured to the patient during treatment and transport. All critical events (drug administration and seizure termination) are logged by verbal statement by the medic on the voice recorder. The box lid switch also monitors against tampering by premature opening of the box, and the temperature sensor monitors drug storage temperatures (important because lorazepam potency is known to be sensitive to extreme storage temperatures).

On EMS arrival at the scene of a patient with ongoing convulsive seizure activity, the medics will perform a rapid initial assessment and stabilization as per their existing protocols. If appropriate and if the patient meets inclusion and does not have exclusion criteria for the study, immediate treatment and enrollment is initiated by opening the study box. Subjects are all immediately treated with the IM syringe, followed immediately by obtaining venous access and treatment with the IV syringe.
Medics provide verbal statements on the voice recorder at the time of IM treatment, at the time an IV is established, at the time of intravenous treatment, at any time convulsions are observed to stop or resume, and at the time of any rescue treatments. The statements are automatically time stamped by the data logger's internal clock. Medics also asked to state whether the subject is seizing on arrival at the ED.

Post-treatment monitoring and treatment in the field. Patients are continuously assessed throughout the period of out-of-hospital management and transport, with vital signs measured at intervals of 5 minutes or less. Assessment includes presence and quality of seizure activity; cardiovascular function (blood pressure, pulse, and cardiac rhythm); respiratory status (respiratory rate, type of airway management, and arterial oxygen saturation by pulse oximetry); and level of consciousness. Online medical command is available to paramedics throughout patients' pre-hospital care. The receiving facility is notified of patient enrollment and an on-call member of the study team is contacted to respond to the ED to complete enrollment of the subject.

In situations where transport time is prolonged, patients with refractory status epilepticus continuing for 10 minutes after the IV study therapy has been delivered, who have not yet arrived at an ED, may be treated with an additional dose of open label benzodiazepine per local EMS protocols if the patient's clinical condition permits such treatment.

Emergency department and inpatient treatment. Due to the range of treatment practices used at the various destination hospitals, a standardized protocol for treating status epilepticus during the emergency department and hospital phases of the study is recommended but not required. The suggested treatment algorithm, shown in Figure 4, specifies timing and doses of lorazepam followed by phenytoin depending on whether seizures continue while the patient is in the ED. The protocol is posted at each destination ED and is also printed on an information sheet provided by the paramedics to ED personnel upon hospital arrival.

Study Activity and Data Collection in the ED. Study materials are collected from the EMS unit on arrival to the ED and the EMS unit is given a new study box in exchange. The study loggers save all data to removable SD data cards. To reset the box, study personnel replace the data card and batteries, restock the study medications per randomization log, and seal the box. Study personnel also approach the subject or family members to provide information about the study and request informed consent to continue data collection in the study.

Collected field materials and case information is collected by a study coordinator. Data from the field materials and case information is entered on a secure web-based case report form with real time validity and range testing. Data files from the logger and digital audio files from the voice recorder are also uploaded to the web-based CRF. Time points are abstracted from the uploaded files centrally at the coordinating center by specially trained and certified study personnel.

Relevance and priority of the study to NETT. This study is ideally suited to the mission and abilities of the NETT network. NETT exists to study the initial emergent phase of treatment by involving those who treat patients with neurological emergencies in the field and on first presentation to the hospital. The trial fundamentally engages pre-hospital and ED investigators in clinical research. The trial will be highly visible and have an immediate impact on clinical practice by determining the optimal treatment of a common emergency by paramedics.

Status epilepticus is a disease state that also represents the broad purpose of the NETT.

![Figure 4. Protocols for treatment of patients after arrival at the destination hospital (from the PHTSE trial). These are suggested but not required for the purposes of the study design (see text). The top panel of the figure shows the general scheme for providing either "rapid"](image-url)

<table>
<thead>
<tr>
<th>Patient seizures</th>
<th>Immediate IV</th>
<th>Phenobarbital</th>
<th>Fentanyl</th>
<th>Place in ED</th>
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<tbody>
<tr>
<td>Seizures recur</td>
<td>Immediate IV</td>
<td>Phenobarbital</td>
<td>Fentanyl</td>
<td>Place in ED</td>
</tr>
<tr>
<td>Standard</td>
<td>Place in ED</td>
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**Details of anticonvulsant drug therapy**

1. Patient seizure(s) occurs on arrival
2. Patient not seizing on arrival, we further assess in ED
3. Patient not seizing on arrival, we proceed in ED

**Figure 4. Protocols for treatment of patients after arrival at the destination hospital (from the PHTSE trial). These are suggested but not required for the purposes of the study design (see text). The top panel of the figure shows the general scheme for providing either "rapid"**
afflicts a wide range of patients including both children and adults. It is particularly morbid in the ever growing elderly demographic. It is common in both men and women, and across ethnic and racial groups.

Furthermore this is a trial that cannot be practicably carried out without the NETT structure and resources. The use of emergency exception to informed consent in this trial, for example, is a critical component of this trial and one that the NETT investigators are well versed. Exception to informed consent for enrollment in emergency research followed by informed consent to continue is likely to be a component of many NETT studies. The investigators of this application have previous experience performing research with exception to informed consent for emergency research, have worked on and authored consensus statements on this mechanism, and have served on IRBs providing review and oversight of traumatic brain injury trials using exception to consent, including working with communities to provide consultation/notification.

**Sample size.** We performed power calculations to determine the sample size using binomial test. We fixed the significance level to be 0.05 and power at 0.8. Based on preliminary studies we conservatively estimate that 70% of subjects will terminate seizure after the initial dose of IV lorazepam. We considered a difference of at least 10% points between the two treatment groups to be important and used it as a minimum detectable difference. To detect this difference, we need approximately 376 subjects per treatment group.

We have therefore planned a study of 800 subjects to be distributed 400:400 into the IM midazolam: IV lorazepam groups. Enrollment will be targeted to 900 subjects to allow oversampling for dropouts.

**Number of clinical centers.** Enrollment in this trial is conducted in 20 Hub clinical sites. Each hub involves one or more local EMS systems and several local receiving hospital Spokes. In the PHTSE trial with essentially the same eligibility criteria, 40 subjects per year were enrolled in a single EMS system. Potential sites for this trial were surveyed and found to treat a mean of 35 ±7 eligible patients per year at the Hubs themselves. We conservatively estimate that Hubs with their Spokes can easily enroll at least 23 subjects per year, allowing the trial to be completed in 24 months.

**Patient selection criteria.** Adult and pediatric patients with continuing seizure activity after EMS arrival and meeting all inclusion and exclusion criteria will be enrolled in this trial. All patients for whom a paramedic ambulance is dispatched are screened for eligibility in the study. Paramedics are instructed to review the complete inclusion/ exclusion criteria (see below) and enroll patients as directed by their on-line or off-line medical control authority.

**Definition of continuing seizures.** For the purposes of emergent treatment, continuous seizures necessitating therapy is defined as convulsive seizures lasting more than 5 minutes. This definition was used to match the standard scenario in which paramedics treat prolonged seizures and is supported by recent recommendations concerning the need for an operational definition of status epilepticus that guides the timing of treatment.

**Inclusion criteria**

1. Paramedics or reliable witnesses verify continuous or repeated convulsive seizure activity of more than 5 minutes, or patient does not regain consciousness (operationally defined as meaningful speech or obeying commands) between seizures.

2. Patient is still seizing on paramedic arrival; or, if not, patient was unresponsive on paramedic arrival and has a qualifying generalized seizure without regaining consciousness (as above).

3. Age greater than 12 months.

**Exclusion criteria**

1. Major trauma as the precipitant of the seizure
2. Immediate need for other IV medication
3. Immediate need for endotracheal intubation
4. Known allergy to midazolam or lorazepam
5. Pulse of <60 beats per minute
6. Systolic blood pressure of <100 mm Hg
7. 2° or 3° atrioventricular block or sustained ventricular tachyarrhythmia
8. Known history of long-term use of benzodiazepines
9. Sensitivity to benzodiazepines
10. Known pregnancy

**Recruitment plan.** Subjects will be recruited upon EMS arrival at the scene of seizing patient meeting eligibility requirements. All participating paramedics will be given face to face training in the conduct of the trial, and provided with resources for online refreshers and reminders. Compliance with enrollment will be monitored through redundant mechanisms including automated online notification systems at hospital arrival, cross referenced to monthly monitoring of EMS dispatch call logs. Enrollments will be reported monthly to all sites in a regular newsletter to reinforce good participations and to encourage sites with lagging enrollment to remediate.
Informed consent process. Consent in this trial is addressed in a two stage process. Subjects are initially enrolled under rules governing emergency exception to informed consent for emergency research (see further discussion below). The study team is immediately notified of treated subjects and completes the second stage of subject enrollment as soon as possible, often in the ED, by determining if the subject (or family or other legally authorized surrogate decision makers) consents to continuing participation in the research. The study team discusses the study with subjects and family, and verbally provides information and answers questions about participation as a subject, and about the rights and responsibilities of subjects and investigators. A comprehensive written informed consent form is used to reinforce the information provided verbally and to document a decision to continue in the study. A copy of this form is provided to the subject and another copy is placed in the research record. Subjects that do not wish to continue to participate are excluded from all further aspects of the study. Previously collected data are excluded for subjects that do not consent to use of such data. Subjects may choose to withdraw consent and discontinue participation in the study at any time.

Emergency exception to informed consent process. US federal regulations and the international Declaration of Helsinki recognize that there are circumstances in which the societal and individual need for medical research on life threatening medical emergencies justifies enrolling subjects in studies even if fully informed consent to participate is not possible because of the nature of the emergency being studied.

This project utilizes the federal regulations that provide guidance for exception from informed consent for emergency research (45 CFR Part 46 and 21 CFR Part 50 updated in October 1996). The project meets the requirements for exception. In brief these are that (1) exception from informed consent is necessary for this project because the need to initiate treatment immediately upon EMS arrival means that there is no time in which to obtain meaningful consent, (2) the disease being studied is life threatening, and (3) the existing therapy is not satisfactory in that obtaining IV access may unnecessarily delay anticonvulsant therapy in all patients, and that IV access may be simply unobtainable in some patients.

In these circumstances, enrollment in clinical research without consent is an ethical and appropriate mechanism as recognized in both US NIH and FDA regulations and by the World Medical Association’s Declaration of Helsinki. Consistent with the federal guidelines, this process requires careful Institutional Review Board review at all participating sites, and extensive community notification. Community notification includes efforts to inform the general public about the study through the local mass media, and outreach through epilepsy support groups and other interested focus groups.

Recent national efforts have defined consensus views on optimal ethical conduct of studies performed using the emergency exception to informed consent. Investigators in this study have participated in and authored these consensus statements. The investigators are committed to ensuring that these processes are carried out in accordance with the highest standards of conduct.

Although there is an exception from consent to initially enroll in this process, formal complete informed consent to continue in the trial will be obtained at the earliest opportunity.

Administration of intervention including dose and duration. This study will examine the administration of a single dose of IM midazolam or IV lorazepam in the setting of pre-hospital treatment of SE.

Adults and children over 50 kg randomized to active IM therapy are treated with 10 mg midazolam IM, and IV placebo. Adults and children over 50 kg, randomized to IV active therapy, are treated with 4 mg lorazepam IV and IM placebo. Study medications and placebo are all prepared in a volume of 4 mL. Children less than 50 kg are treated with a dose determined by a Breslow tape modified for this study and included in each kit that shows the dose in mL to be given for each route of administration for pediatric subjects by estimated weight based on their length (IM midazolam 0.2 mg/kg, IV lorazepam 0.1 mg/kg).

Extent and type of blinding/masking. This is a blinded study. Patients and paramedics are blinded to the treatment assignment as are the investigators that abstract the primary and secondary outcomes off the data logger and voice recorder. The code will only be broken after the subjects’ data record is complete.

Blinding is provided by the use of an IV and an IM syringe in every subject. Since every subject receives both active drug and a placebo dummy, the subject, the treating paramedic, and the receiving facility emergency department remain unaware of the treatment assignment.

Follow-up plan. Clinical data including scanned primary source material from the hospital treatment and disposition are collected by local study
investigators and reported on an on-line case report form with real time validity checking and data queries. Central data monitoring is performed at enrollment by the study Clinical Coordinating Center, and confirmed at site monitoring visits.

Outcome data is collected centrally at the Clinical Coordinating Center’s Outcome Monitoring Unit. Trained and certified researchers in this unit perform structured telephone interviews with subjects that are validated for assessment of modified Rankin score (mRS) and quality of life scores. These researchers also abstract time, location, treatment, and temperature data provided electronically from the kit data loggers.

**Endpoints and outcomes.**

**Primary outcome measure.** The primary outcome measure is the binary outcome variable measuring whether or not there is termination of seizure prior to arrival in the ED after an initial dose of study medication without the need for a second “rescue” dose of benzodiazepine by EMS.

Termination of seizures is considered to have occurred at ED arrival if major motor convulsions have stopped, unless the patient continues to be unresponsive and has an electroencephalogram (EEG) documenting ongoing electrical seizure activity or has subsequent clinical seizure activity for which specific anticonvulsant drug treatment is given. Determination of termination of seizures is made by the attending emergency physician treating the subject upon arrival at the receiving emergency department.

Successful use of these outcome measures have been previously demonstrated in the PHTSE trial.\(^3\)

**Secondary outcome measures.** Key secondary outcome measures include times from EMS arrival and initiation of treatment to termination of seizure. Other secondary outcomes include use of rescue benzodiazepine by EMS prior to arrival at the hospital, acute recurrence of seizures in the hospital, neurologic outcome at 90 days, frequency of subsequent endotracheal intubation, and frequency of subsequent ICU admission.

EMS arrival is determined by the GPS unit in the study medication box data logger. Time of arrival is defined as the first time the data logger arrived within an estimated 100 foot radius of the location where the box was subsequently opened.

Initiation of treatment is determined by the voice recorder in the study medication box data logger and is defined as the time the paramedic initiates a verbal confirmation of the study medication being given.

Termination of seizure is determined by the voice recorder in the study medication box data logger and is defined as the time the paramedic initiates a verbal confirmation that major motor convulsions have stopped, unless the patient subsequently is given another dose of benzodiazepine by EMS or is determined not to have termination of seizure on ED arrival.

Neurologic outcome at 90 days is determined by modified Rankin scale (mRS). The mRS is scored from a structured telephone interview with the subject or the primary care giver for the subject, conducted by a certified evaluator at the clinical coordinating center. The evaluator is blinded to patient treatment.

Endotracheal intubation performed or attempted by EMS or within 30 minutes after ED arrival is abstracted from the ED record physician and nursing records.

ICU admission from the ED is abstracted from the hospital admission record. This is scored as occurring only if the ICU is the initial inpatient unit for the patient.

Etiology of the status epilepticus episode is abstracted from the discharge summary as recorded in the medical record. The cause of the status epilepticus episode is determined on the basis of the patient’s history and results of diagnostic testing. Because the etiology of status epilepticus can independently affect response to anticonvulsant drug therapy and patient outcome, it is evaluated as a confounding factor for relevant outcome measures. On the basis of available literature, we grouped etiologies with regard to their effect on outcome and treatment response prognoses as follows. Favorable: remote symptomatic (includes patients with a history of recurrent unprovoked seizures), alcohol-related, nonepileptic seizures. Intermediate: drug toxicity, central nervous system infection, trauma, central nervous system tumor, metabolic derangements. Poor: anoxia or cardiopulmonary arrest, or stroke.

**Statistical methods to analyze primary and secondary outcomes.** Primary and secondary outcomes are analyzed on an intention to treat basis. We will first clean the data by looking at the distributions and checking for the outliers etc without unblinding the data. To the extent possible, unblinding will be maintained until the final sets of analyses have been planned. Most primary and secondary outcomes are binary. We will use
binomial test to compare the two proportions. If the sample sizes are large, we will use large sample chi-square approximations. Time to termination of seizure will be analyzed using Kaplan-Meier approach and log-rank tests.

Secondary analyses will also examine the potentially confounding effects of the etiology of status epilepticus, the duration of status epilepticus prior to study drug treatment, and the length of the interval between study drug treatment and emergency department arrival.

We will use logistic regression modeling to estimate treatment effects on the primary and adjust for the effects of covariates. The primary analysis is restricted to unique (first enrollment) cases, but secondary analyses of data from subjects with multiple enrollments use the generalized estimating equations approach to account for correlation between observations. This approach enables us to carry out analyses that yield valid variance estimates for the multiple enrollments. The logistic models will use the binary indicator of status epilepticus as the outcome and a binary indicator to describe each of the treatments (IV lorazepam and IM midazolam), and allow for the inclusion of other significant covariates.

Continuous variable (e.g., transport time to the ED) will be compared between the treatment groups using analysis of variance; ordinal categorical variables (e.g., etiology of status episode) will be compared using Kruskal-Wallis tests; and nominal categorical variables will be compared using chi-square tests. Variables showing imbalances in these variables between the two treatment groups will be used as covariates in the logistic models provided they are affected by the treatment. The association of each covariate with the outcome will be assessed by fitting logistic models with each covariate singly first and then a multivariate logistic model will be used to obtain adjusted treatment effect as measured by the odds ratio.

The fit of the logistic models will be assessed with the Hosmer-Lemeshow goodness-of-fit test and regression diagnostics. If there is a substantial lack of fit, techniques such as transformations of covariates will be used to improve the fit.

Randomization. Subjects will be randomized to IM midazolam or IV lorazepam in 1:1 manner. Randomization will be in blocks by study site and EMS crew. Kits are distributed to EMS crews by block randomization. Subjects are allocated to treatment group by the kit carried by the EMS crew.

Interim monitoring plan A Data Safety Monitoring Board appointed by the NINDS will provide ongoing evaluation of adverse events, and will perform interim monitoring of primary and secondary outcome measures. The Data Safety Monitoring Board will be formed by the NINDS as per institute guidelines. Members of the clinical coordinating center and the statistical coordinating center will provide data to and support for the DSMB at scheduled intervals and as requested. It is anticipated that the NINDS will convene the DSMB for face-to-face meetings in Bethesda annually, and that other scheduled reviews can be performed by teleconferencing.

At a minimum, Interim safety analyses will be performed after enrollment of every 50 subjects, but additional interim analyses may be added by the DSMB at their discretion. The trial will be stopped early if there is compelling evidence of toxicity or risk as determined by the DSMB at their discretion, or if they find the interim analyses meet any of the predefined stopping criteria.

Data 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”.

All serious adverse events occurring during the 90 days of study participation will be documented. A serious adverse event is one that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, or any event that the treating clinician or internal medical monitor judges to be a significant hazard, contraindication, side effect, or precaution. The internal medical monitor will review all cases of possible adverse events and report them to the DSMB and the principal investigator. Adverse events will be reported to all Institutional Review Boards. For each serious adverse event, the medical monitor will be asked to classify the causal relationship of the event to the study treatment as probable, possible, unlikely, and unrelated.

Serious Adverse Events and Adverse Events that will be tracked include: death, injection/infusion site complications, respiratory arrest, hypotension (SBP<90 mmHg), and recurrent status epilepticus.

Ethical and consent considerations. This Human Subjects Research meets the definition of a clinical trial. This study will be conducted in accordance with current U.S. Food and Drug Administration...
(FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

Analysis of risk and benefit. The risks and benefits for subjects enrolled in this trial of participation are appropriately balanced. Subjects randomized to IM treatment may benefit from earlier termination of their SE than is possible with IV therapy, but may have slower termination of their SE if IM treatment is less effective than IV. With regard to subjects randomized to IV therapy, risks are likely to be similar in both groups and consistent with or favorable as compared to currently existing EMS protocols.

Specific Compliance with Exception to Informed Consent Regulations. Due to the emergent nature of status epilepticus and the unconscious state of the patient at the time of treatment, subject enrollment and administration of study drug are performed under emergency exception to informed consent for research. Strict compliance with federal regulations ensures protection of subjects enrolled in this manner. A second phase of the process occurs at the earliest opportunity, once the subject has regained consciousness or family members have been contacted. At this time, a standard informed consent process is used to determine and document whether the subject wishes to continue participation in the study (including follow up evaluation and review of medical records).

IRB review at each participating institution is required to demonstrate compliance with the conditions set out for emergency exception to informed consent in the Federal Regulations (21 CFR Part 50). The specific components of the regulations are enumerated and reasons for waiver of consent are detailed in section E of the NETT grant.

Community notification about the study. Community notification ensures that the conduct of trials with exemption to consent is a transparent and open process. It assures that investigators are willing to publically explain and visibly take responsibility for how these trials are conducted. Notification for this trial includes efforts to target patients with known seizure disorders, and efforts to inform the general population. The targeted efforts involve presentations and written materials distributed to patients and their families at participating epilepsy clinics, epilepsy advocacy organizations, and at epilepsy support groups. To reach the community at large, the trial is presented through local media outlets by press release, public service announcement, and advertisements. Whenever possible, these efforts are coordinated with the participating media relations departments, and other medical center and disease advocacy campaigns.

Potential benefits of the proposed research to the subjects and others. The potential direct benefit of this research to subjects that receive IM midazolam is that this treatment may shorten the time to termination of seizures by eliminating the need for IV access to be obtained prior to treatment. Faster control of seizures is thought to reduce the risk of refractory status epilepticus, and may result in improved neurologic outcomes. Subjects that receive IV lorazepam may also directly benefit from participation in this trial. Although lorazepam is currently the preferred intravenous benzodiazepine for use in the treatment of acute seizures in the ED, logistic barriers to its use prevent its widespread use in most EMS systems. By managing those barriers, subjects in the lorazepam group are provided access to a potentially more effective agent that if they were treated by existing protocols that most often use diazepam.

The knowledge to be gained in this trial is important and immediately applicable to how paramedics treat patients with status epilepticus every day. Identification of a more rapid, effective non-intravenous route of treatment, with midazolam, a stable and affordable medication in US EMS systems, would immediately affect paramedic practice. Furthermore, the knowledge to be gained in this trial is important to emergency preparedness efforts directed at the possible deployment of a nerve gas attack by terrorists, such as the sarin release that occurred in the Tokyo subway system. Pre-clinical data suggest that early control of seizures is important to reducing the mortality after such exposures, and demonstration of efficacy of IM midazolam in status epilepticus would inform plans to respond to possible mass casualty situations in which large numbers of victims may suffer seizures.

Participating pharmaceutical or device manufacturing company and IND/IDE status or FDA exemption. This trial studies two medications that are already FDA approved and used clinically in the treatment of SE. Together with the pharmaceutical manufacturing companies Roche and Baxter, makers of midazolam and lorazepam respectively, we are investigating the need for an IND for the application under investigation in this trial.

Literature Cited


