Pediatric Dose Optimization for Seizures in EMS (PediDOSE)
PECARN Protocol Number 052

Pediatric Emergency Care Applied Research Network
National Institute of Neurological Disorders and Stroke (NINDS)
Health Resources and Services Administration (HRSA)
Maternal and Child Health Bureau (MCHB)
Emergency Medical Services for Children (EMSC) Program

Protocol Version 1.05
Version Date: March 10, 2023
Printing Date: March 10, 2023
IND: 156119
NCT: 05121324

This protocol is PECARN Protocol Number 052, and has been authored by Manish I. Shah, M.D., M.S., Baylor College of Medicine, for implementation with the PECARN investigators. This study is supported by U01-NS114042 awarded to Baylor College of Medicine (PI:Manish I. Shah, M.D., M.S.) by the National Institute of Neurological Disorders and Stroke (NINDS).

The PECARN research network is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS), in the Maternal and Child Health Bureau (MCHB), under the Emergency Medical Services for Children (EMSC) program through the following cooperative agreements: DCC-University of Utah (UJ5MC30824), GLEMSCRN-Nationwide Children's Hospital (U03MC28844), HOMERUN-Cincinnati Children's Hospital Medical Center (U03MC22684), PEMNEWS-Columbia University Medical Center (U03MC00007), PRIME-University of California at Davis Medical Center (U03MC00001), CHaMP node – State University of New York at Buffalo (U03MC33154), WPEMR – Seattle Children's Hospital (U03MC33156), and SPARC- Rhode Island Hospital/Hasbro Children's Hospital (U03MC33155). This information or content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.

This document was prepared by the PECARN Data Coordinating Center (DCC) located at the University of Utah School of Medicine, Salt Lake City, Utah. The document was written and typeset using LaTeX 2_ε. The DCC at the University of Utah is supported by Cooperative Agreement UJ5MC30824 from the Emergency Medical Services for Children (EMSC) Program, Maternal and Child Health Bureau, Health Resources and Services Administration.

PROTOCOL TITLE:

Pediatric Dose Optimization for Seizures in EMS

Short Title: PediDOSE
PECARN Protocol Number: 052

Lead Investigator and Author:
Manish I. Shah, M.D., M.S.
Baylor College of Medicine

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Seizures are one of the most common reasons why bystanders call Emergency Medical Services (EMS) for a child, and current practice frequently fails due to under-dosing and delayed delivery of anti-seizure medication. Benzodiazepines, such as midazolam, given in the nose or as a muscular injection are the first line treatment for seizures. Unfortunately, one-third of children having a paramedic-witnessed seizure have ongoing seizures on arrival to the emergency department (ED) because an inadequate and delayed dose of midazolam fails to stop seizures. Children who continue to seize have seizures that are harder to stop, and this puts them at risk for not breathing and having brain damage. Reducing this risk requires equipping paramedics with a simplified method for rapidly determining and administering a therapeutic dose of medication. Paramedics suggest simplifying midazolam dosing by eliminating the error-prone, sequential calculations required to determine a weight-based dose under stressful conditions. Standardized, age-based dosing may be simpler, faster and more effective, without compromising safety.

The overall objective of the Pediatric Dose Optimization for Seizures in EMS (Pedi- DOSE) study is to measure the impact of standardized EMS midazolam dosing on seizure treatment effectiveness and safety. To achieve this objective, we will conduct a large EMS trial in the Pediatric Emergency Care Research Network (PECARN) to implement standardized, age-based midazolam dosing for pediatric seizures in EMS systems in 20 cities. We believe that implementation will stop more seizures before children arrive at EDs without increasing respiratory failure rates. The first aim of this study is to compare the impact of standardized EMS midazolam dosing relative to conventional dosing on seizure cessation. We hypothesize that giving a standardized midazolam dose based on age will allow paramedics to stop a child's seizure faster than conventional dosing with current practice. The second aim of this study is to determine how often children stop breathing or ineffectively breathe after implementation of standardized EMS midazolam dosing. We hypothesize that standardized EMS midazolam dosing will be associated with no difference in slow or absent breathing relative to conventional dosing with current practice. If this study demonstrates that standardized, age-based midazolam dosing is both safe and more effective than current practice, the potential impact of this study is a paradigm shift in the treatment of pediatric seizures that can be easily implemented in emergency medical services (EMS) systems across the country.

1 Study Summary

This study is a Phase 3, multi-center, stepped wedge trial of midazolam dosing for seizures in pediatric patients in the Emergency Medical Services (EMS) setting. It randomizes the timing of each of the participating EMS agencies at 20 different sites to switch from conventional, weight-based dosing to standardized, age-based dosing, so that every EMS agency switches from conventional to standardized dosing over a 4-year enrollment period in this 5-year study. Federal exception from informed consent (EFIC) procedures will be used for enrollment.

1.1 Study Objective and Outcomes

Aim 1 - Primary Objective (Effectiveness)

The primary objective of this study is to compare the impact of standardized EMS midazolam dosing on seizure cessation. We hypothesize that standardized intramuscular (IM) or intranasal (IN) midazolam dosing of approximately 0.2 mg/kg, based on age-based estimates for weight, will be associated with lower frequency of active seizures upon ED arrival, when compared to conventional dosing with calculations from estimated weights.

Aim 2 - Secondary Objective (Safety)

The secondary objective of this study is to compare the frequency of respiratory failure after implementation of standardized EMS midazolam dosing for pediatric seizures. We hypothesize that standardized dosing will not increase respiratory failure when compared to conventional dosing.

1.1.1 Primary Outcome

The primary outcome is the proportion of patients having a seizure on ED arrival. To assess the primary outcome in patients who are completely unresponsive to verbal or painful stimuli, a rapid response electroencephalogram (EEG) recording device will be applied to children in whom the device is approved by the Food and Drug Administration (FDA), which is currently cleared for use in ages 2–13 years old. Once the device is FDA-cleared or approved for use in 6–23 month olds, it will also be applied to these study-eligible participants.

1.1.2 Secondary Outcomes

The two secondary outcomes are:

- Proportion of patients with respiratory failure in the prehospital setting or within 30 minutes of ED arrival, defined as having received bag valve mask (BVM) ventilation, bi-level positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), or placement of a supraglottic airway (SGA) or endotracheal intubation (ETI);
- Time to first midazolam administration after paramedic arrival to the scene.

1.1.3 Exploratory Outcomes

Exploratory outcomes include:

- Time to seizure cessation in the ED, if still having a seizure on ED arrival;
- Dose/route adherence, defined as receiving an intranasal (IN) or intramuscular (IM) midazolam dose within 30% of 0.2 mg/kg (0.14–0.26 mg/kg), calculated from the measured ED weight.

1.1.4 Safety Outcomes

Safety outcomes include:

- Life threatening hypotension

- Life threatening cardiac arrhythmia
- Depressed level of consciousness

2 Rationale and Background

Emergency Medical Services (EMS) frequently transports children with active seizures children, but treatment delays make seizures difficult to stop and lead to respiratory failure, brain damage and death.[1, 6, 7, 13, 23, 26, 31, 34, 36] Immediate delivery of the correct benzodiazepine dose is essential to effectively and safely treat pediatric prehospital seizures, and an evidence-based guideline (EBG) recommends the initial use of intramuscular (IM) or intranasal (IN) benzodiazepines over other routes, since obtaining intravenous (IV) access is time-consuming and challenging during an active seizure.[6, 13, 17, 21–23, 30]

Our prior work has shown that paramedics are more likely to administer the first dose of midazolam via the preferred IN/IM routes after implementing a protocol consistent with the EBG. However, dosing errors, treatment failure (still having a seizure upon ED arrival), and delays in benzodiazepine administration after scene arrival are still common.[31] Paramedics have suggested that making equipment available for IN/IM medication administration, standardizing doses for preferred routes, eliminating dose calculations, and removing protocol ambiguities would enhance protocol adherence and improve outcomes.[3]

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) evaluated standardized doses of IV lorazepam and IM midazolam in adults and children approximately 2 years and older, and the results from RAMPART weighed heavily in the EBG recommendations.[32] Though the focus of RAMPART was to compare different routes of benzodiazepines in terminating status epilepticus before ED arrival, it also demonstrated that standardized dosing is feasible in children, though larger pediatrics studies are needed.[32] Other studies have demonstrated that midazolam at IN/IM doses of 0.2–0.5 mg/kg are effective and safe in children in the ED, but this has not been studied in a prehospital setting.[11, 25, 28] In EMS, the high rates of pediatric under-dosing and high frequency of seizures on ED arrival highlight how optimizing dose administration could improve outcomes. A potentially more effective approach than current practice is to eliminate calculations through standardized, volume-based dosing based on a child's age[15, 16, 19, 20, 33] Since respiratory failure may be due to prolonged status epilepticus rather than benzodiazepine overdose, using this standardized approach may also be significantly safer than conventional dosing.

3 Subject Eligibility, Accrual and Study Duration

3.1 Eligibility criteria.

Inclusion criteria for the EMS treatment protocol are:

- Age ≥ 6 months* to ≤ 13 years; AND
- Witnessed by a paramedic to be having a seizure, regardless of seizure type or duration; AND
- Transported by an EMS agency participating in this study.

*(The lower age limit eligible to receive the standardized midazolam dose will be iteratively modi-

fied using an age de-escalation approach, described in more detail below. All patients in the age range noted above are eligible for study inclusion, regardless of whether the EMS agency is using conventional dosing or standardized dosing at a given point in time.)

Exclusion criteria are:

- A prior history of a benzodiazepine allergy; OR
- Known or presumed pregnancy; OR
- Severe growth restriction based on the paramedic's subjective assessment.

Age will be determined based on the bystander's report to the paramedic at the scene. If the bystander does not know the patient's age or no bystander is present, the paramedic will use whatever length-based tape the EMS agency uses to estimate the age.

3.2 Subject Accrual and Study Duration

PediDOSE utilizes a stepped wedge design to randomize PECARN EMS affiliates in 20 cities to implement standardized dosing in a staggered manner, every four months. Subject accrual will occur over four years. We anticipate that we will enroll up to 6,700 subjects over this four year period.

3.3 Age De-escalation

For the doses utilized in the EMS protocol for the intervention, we will use an age de-escalation strategy to balance the need to maximize safety in the youngest pediatric patients while also generating evidence on the effectiveness of standardized, age-based dosing in these patients.

At the beginning of Year 1 of patient enrollment, all sites will utilize conventional dosing in their EMS agencies. Conventional dosing is what the EMS agency is already doing to determine the dose before the study begins, and agencies typically use manual calculation of the midazolam dose based on the patient's weight, using an estimate from a length-based tape, followed by conversion of that dose to a volume to be administered.

When the initial sites implement standardized dosing in Year 1, they will do so only for 2–13 year old patients; any patient <2 years old will still continue to be dosed according to conventional dosing. Standardized dosing utilizes a dose of approximately 0.2 mg/kg IN/IM midazolam and eliminates all calculations, since the volumetric dose is based on the bystander-reported patient age. For the study, all EMS agencies will utilize the 5 mg/ml concentration of midazolam in order to standardize the age-based volume of medication that is administered via the IN or IM routes across all sites.

Near the end of each year of enrollment, the data safety monitoring board (DSMB) will evaluate patient safety data on those already enrolled to determine if it is safe to de-escalate the age in the subsequent year(s) of enrollment (Years 2, 3, and 4). If the DSMB approves de-escalation for the upcoming year(s) of enrollment, the EMS agencies that subsequently implement standardized dosing will use the revised lower age limit for standardized dosing. All EMS agencies that had already

implemented standardized dosing must begin utilizing the revised lower age limit within 12 months of DSMB approval; this additional time is allowed so that the EMS agency can coordinate the change with their usual periodic, system-wide patient care protocol updates. In-person paramedic training will not be required when age de-escalation occurs in EMS agencies that have already switched to standardized dosing. Online/printed EMS protocols and decision support tools will be updated to reflect the change. Paramedics will also be notified of the change in accordance with their EMS agency's communication policy regarding protocol updates.

At the beginning of Year 3 of patient enrollment, if the DSMB deems that it is safe to do so based on data from patients already enrolled, a fourth dose of midazolam (1.25 mg = 0.25 mL) will be added for 12–16 month old patients. The lower age limit of enrollment will then decrease to 6 months at the beginning of Year 4 of patient enrollment, if the DSMB deems that it is safe to do so. By the end of the 4-year patient enrollment period, all sites will have switched from conventional to standardized dosing for doses and age ranges that the DSMB has determined to be safe.

Data will be collected on all eligible 6 month to 13 year old patients during the entire enrollment period, regardless of the status of age de-escalation, because younger patients who are being treated based on conventional dosing are part of the comparison group relative to those being treated under the clinical EMS treatment protocol that utilizes standardized midazolam dosing. Collecting data on these younger patients at all phases of the study is necessary to sufficiently answer the study question, even if they are being treated using conventional dosing.

The overall age de-escalation strategy is summarized below:

Table 1: Age de-escalation strategy.

Age	Year of Patient Enrollment	Estimated % of Pediatric Patients Having a Seizure Who Are Eligible for PediDOSE	Standardized Dose for PediDOSE
12–13 years	**Year 1**	**8%**	**10 mg = 2 mL**
6–11 years	**Year 1**	**47%**	**5 mg = 1 mL**
2–5 years	**Year 1**	**36%**	**2.5 mg = 0.5 mL**
17–23 months*	**Year 2**	**4%**	**2.5 mg = 0.5 mL**
12–16 months*	**Year 3**	**2%**	**1.25 mg = 0.25 mL**
6–11 months*	**Year 4**	**3%**	**1.25 mg = 0.25 mL**

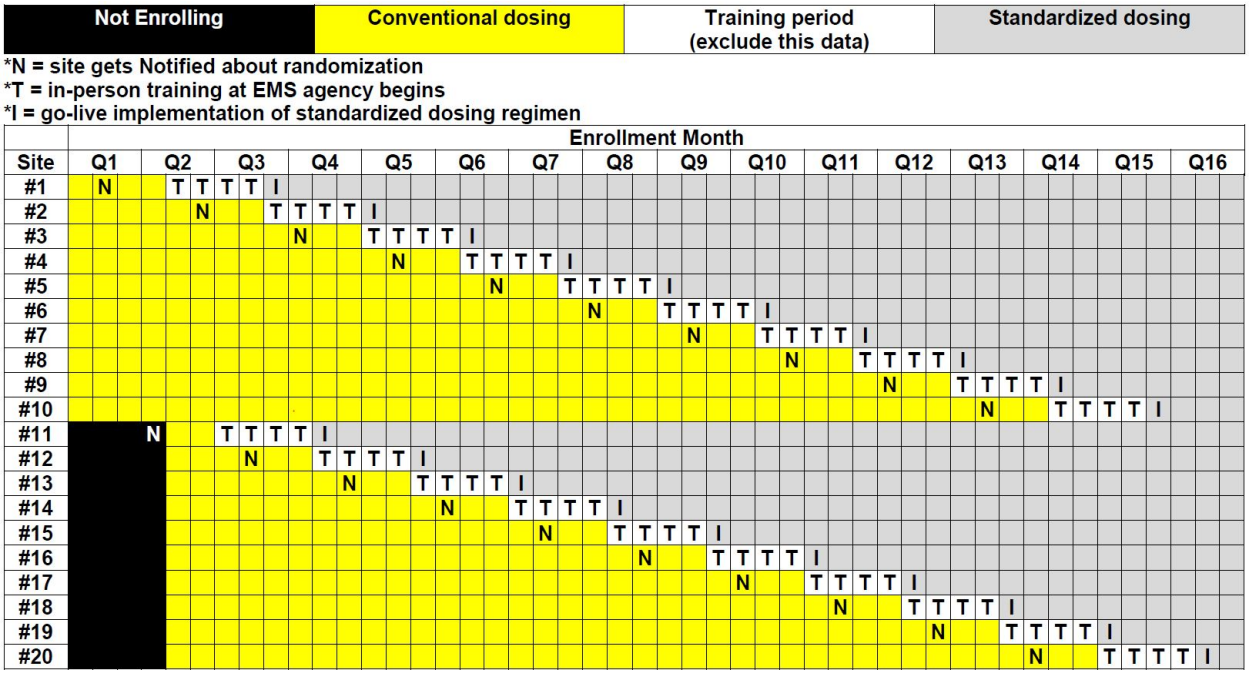
*Contingent upon DSMB approval after evaluation of patient safety data

4 Study Procedures

4.1 Stepped Wedge Design and Randomization of EMS Agencies

PediDOSE utilizes a stepped wedge (SW) design (Figure 1 on the following page) among the PECARN EMS affiliates to implement standardized dosing in a staggered manner at an agency, every 2 months.[12] Due to the timing of EFIC, the stepped wedge will be implemented in two stages of 10. With the SW design, standardized dosing will be staggered at all 20 sites after a 4-month training period.

Figure 1: Stepped wedge design and study timeline.



The stepped wedge design randomizes the order in which the sites will transition from conventional to standardized dosing within the sites of each cohort (the sites that start earlier and the sites that start later). Following the approximate timeline in the figure, approximately every 4 months per cohort of enrollment, the PECARN DCC will provide notification about randomization to a city's participating EMS agencies to make the change from conventional weight-based dosing to standardized age-based dosing. No individual patient randomization will occur. The allocation will be concealed regarding the timing of when the EMS agency will switch from conventional to standardized dosing, such that agencies and investigators will not know when their transition will occur until they receive notification about randomization. In order to allow for the system-wide changes required for implementation, the EMS agency leadership, other site personnel, and the study PI will be informed up to 2 months prior to beginning the 4 month training period, after which the new protocol will be implemented. The ED staff may be aware of the randomization status of the local EMS agency or agencies participating in the study.

4.2 Identification of Patients

In many instances, the research coordinator (RC) will be present in EDs directly affiliated with the study when the EMS agency transports the child, and they will screen EMS arrivals for eligible patients. We will attempt to gather EMS data about children who were transported to non-affiliated emergency departments (EDs) for a seizure to determine trial eligibility. A non-affiliated ED is defined as other EDs in metropolitan areas where the study is occurring that lack research coordinator (RC) coverage for this study. To assure data capture when the RC is not available to have a direct conversation with the paramedic after patient hand-off, or when the patient is

transported to a non-affiliated ED, the paramedics will either call a phone number that they can access anytime to notify research staff that they have transported a potentially eligible patient or by direct data entry link. Data that is collected directly from the paramedic about the prehospital care of the enrolled patient is referred to as the "paramedic self-report." The study staff will verify eligibility criteria when they obtain this paramedic self-report either in-person, over the phone, or by direct data entry by the paramedic.

Since it is possible that the paramedic may not have a chance to directly communicate with the RC between patient hand-off and when they go back into service, the RC will also review daily data from the EMS agency database to identify patients who are potentially eligible to be included in the study. Agencies that do not provide database access to their affiliated hospital will securely transfer data for all pediatric seizure transports to the coordinator and site investigator for the purpose of eligibility screening. The RC will review the limited EMS data necessary to confirm that the patient meets all inclusion criteria, including verification that they were having a seizure in the presence of a paramedic. These patients will be included in the DCC database, and if exclusion criteria are present, those criteria will also be included in the DCC database. Eligible patients who meet all eligibility criteria will have data collected in accordance with the choice that their parent, guardian, legally authorized representative or other adult family member has made during the therapeutic time window or at the time of trial notification, as described in Section 5.

4.3 Study Arms

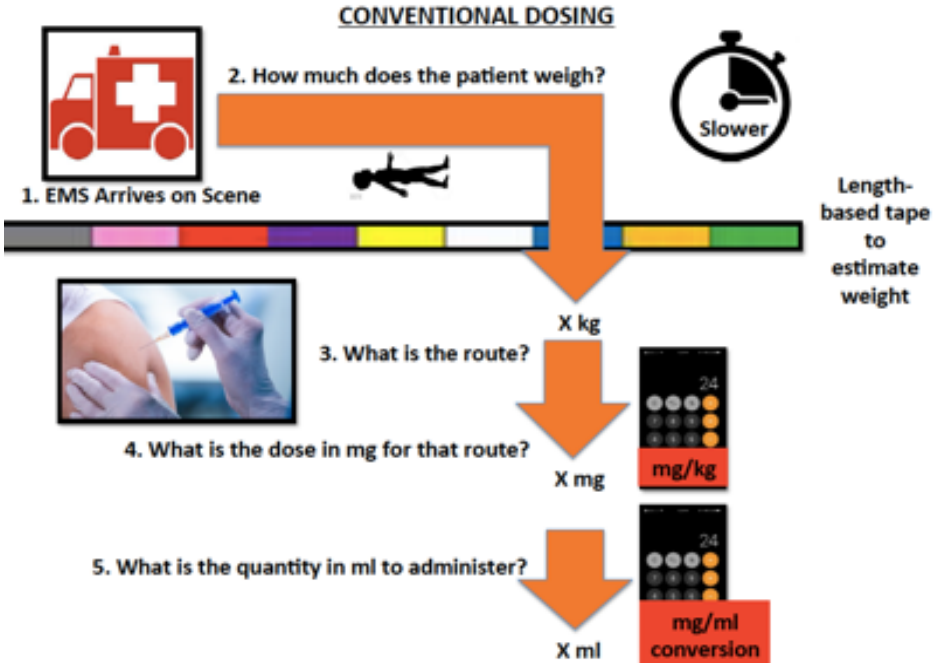
The two study arms are schematically shown in Figure 2 on the following page. In the conventional dosing arm (a), EMS agencies will continue to utilize the weight–based drug dosing method that is part of current practice in accordance with their existing EMS protocol. Typically, paramedics determine a patient's weight using whatever system their EMS agency uses (Broselow, Handtevy or other mechanism), choose a route of administration [IM, IN, IV, or intraosseous (IO)] and perform several calculations to determine the dose of medication to deliver. The standardized dosing arm (b) reduces the choice of routes to IM or IN, and eliminates calculations of drug dose. The drug dose is based on age of the child, as determined from bystanders or estimated by the paramedic.

All participating EMS agencies have agreed to continue their current protocol until randomization, and to use the standardized dosing regimen after randomization, training and implementation. The standardized midazolam dose is approximately 0.2 mg/kg (range: 0.14–0.26 mg/kg), based on the published EBG for pediatric seizure management.[30] The four dose options ensure the weight-based dose is within 30% of the 0.2 mg/kg EBG-recommended dose. The estimated doses for the proposed study are based on the 50th percentile weights-for-age from standardized Centers for Disease Control growth charts. After implementation, a sticker, card, and/or other decision support tool compatible with what paramedics already access in their EMS agency for dosing guidance will be located in proximity to where the midazolam is stored, so that the standardized doses for each age range are readily available when drawing up the medication.

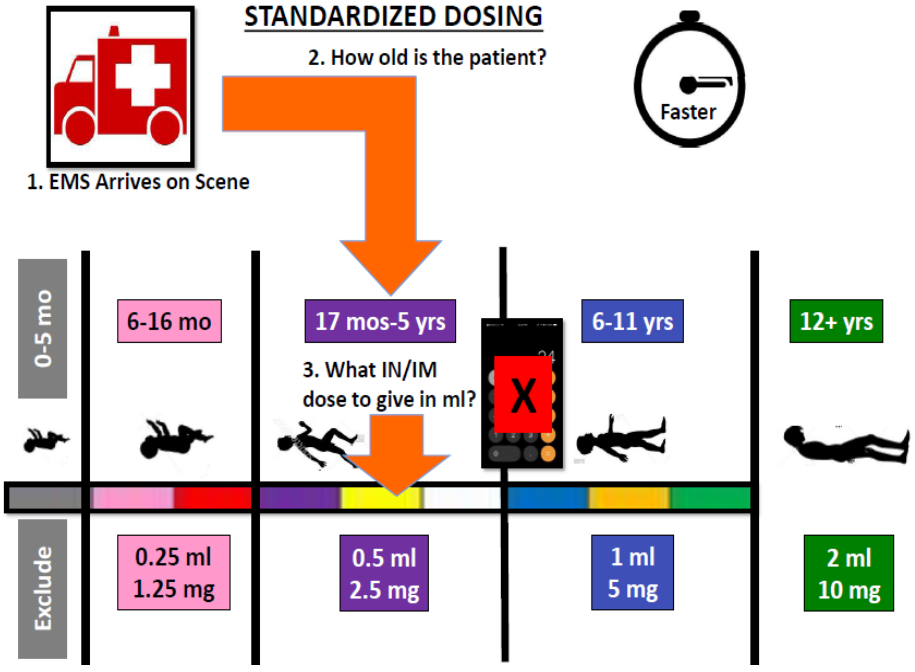
5 Data Collection

The sources of all data variables that will be collected are shown in Table 2 on page 17. Data to be collected for this study includes:

Figure 2: Study arms being assessed in PediDOSE trial.



(a) Conventional treatment (control).



(b) Standardized treatment (intervention).

- Prehospital Data from both the EMS database and the paramedic self-report: To be collected for all enrolled patients regardless of destination of transport
- Hospital Data including rapid response electroencephalogram (RR-EEG) and hospital records: To be collected for all patients transported to a hospital affiliated with the study.
- Publicly available data: To be collected, as needed, to confirm mortality information for participants who died and access to hospital records is not available to investigators due to withdrawal or transportation to a non-affiliated ED.

Parents, guardians, legally authorized representatives, and adult family members may have the opportunity to decline trial participation during the therapeutic time window, if feasible, and will have the opportunity to decline ongoing trial participation, including data collection, at the time of notification about the trial. If a parent, guardian, legally authorized representative, or adult family member declines further data collection, this date/time will be noted on the informed consent document and no data will be collected after the date/time of participant withdrawal. If, despite the investigator's best efforts, the investigator is not able to contact a parent, guardian, legally authorized representative, or adult family member during the therapeutic time window and notification about the trial at the earliest feasible opportunity is not successful, participant data will be collected as described above.

5.1 Prehospital Data Collection

5.1.1 EMS Database

Paramedics already capture the majority of EMS data necessary for this study during usual documentation of patient care in the EMS agency's electronic medical record. For sites that do not have direct access to this data, the EMS agency will securely transfer the data for all pediatric seizure transports to the study team regularly. The research coordinator at the site will enter relevant information into a secure electronic data capture (EDC) system that is housed at the PECARN Data Coordinating Center (DCC), based at the University of Utah. Data from the EMS record includes variables such as dates and times of the incident, medication administration, patient demographics and past medical history.

Table 2: PediDOSE data variables and sources.

PediDOSE Data Variables and Sources

Collected if transported to any emergency department (ED)	**X**	**X**		
Collected if transported to EDs affiliated with the study	**X**	**X**	**X**	**X**
Variable	**Data Source:** EMS Database	**Data Source:** Paramedic Self-Report	**Data Source:** Hospital Record	**Data Source:** ED Rapid Response EEG
Incident run number	X	X		
Paramedic-witnessed seizure	X	X		
Exclusion criteria: benzodiazepine allergy, pregnancy, or small for age	X	X	X	
Date/time of EMS call	X			
Date/time EMS dispatched to scene	X			
Date/time paramedic arrived on scene	X			
Date/time paramedic arrived to the patient	X			
Date/time EMS departed the scene	X			
Total on-scene time (= scene arrival time – scene departure time)	X			
Address	X			
Date/time of 1st midazolam dose [C]	X	X		
Route of 1st midazolam dose [D]	X	X		
Patient received 1st midazolam by the preferred IN or IM routes [D]	X	X		
Amount of midazolam dose(s) [D]	X	X		
EMS doses given [D]	X			
Bystander benzodiazepines given	X	X		
Paramedic method of dose determination		X		
Seizure characteristics		X	X	
Estimated/reported EMS weight	X			
Past medical and family history relevant to seizures		X	X	
Maximum temperature during EMS care or within 6 hours of ED arrival	X		X	
Blood pressures	X		X	
Heart rate	X		X	
Glasgow Coma Score (GCS) or level of responsiveness		X	X	
Blood glucose	X		X	
Arrhythmias and/or CPR, defibrillation, cardioversion, pacing performed	X		X	
Respiratory failure	X	X	X	
Patient sex	X		X	
Patient's preferred language			X	
Patient race	X		X	
Patient ethnicity	X		X	
Patient name [A]	X	X	X	
Destination of transport [A]	X	X	X	
Patient age [A]	X	X	X	
Date/time EMS arrived at the ED [A]	X	X	X	
Parent/guardian name, phone number		X	X	
Paramedic name(s), phone number, age, years of experience		X		
Seizure on ED arrival assessed by paramedic, nurse, physician, EEG [B]		X	X	X
Time rapid response EEG data transmission began				X
Time of seizure cessation (if still seizing on ED arrival) [D]			X	X
Seizure cessation or recurrence	X	X	X	X
ED weight [D]			X	
Other anti-seizure medications and IV fluids given	X	X	X	
Other medications given in response to an adverse event			X	
ED length of stay			X	
Diagnoses that may be confounders or effect modifiers for seizures	X		X	
Hospital length of stay			X	
Total treatment time (=scene arrival time – hospital discharge time)	X		X	
Disposition from the ED and hospital			X	

[A] Used to **link** EMS and hospital records
[B] Used to assess the **primary** outcome
[C] Used to assess a **secondary** outcome
[D] Used to assess an **exploratory** outcome

5.1.2 Paramedic Self-Report

Upon arrival to the ED, a study-affiliated research coordinator, if present, will collect paramedic self-reported data not routinely documented in the electronic EMS record. If the paramedic arrives at an ED where the coordinator is not available, the paramedic will get in touch with the research staff by either calling a phone number or via direct data entry using a QR code or link.. Both the phone number and the QR code will be accessible on all paramedic vehicles, so that they can notify research staff anytime that they have transported a potentially eligible patient. The study staff will verify eligibility criteria when they obtain this paramedic self-report either in-person, over the phone, or online in REDCap. The paramedic self-report will also include questions about whether it was feasible or not for the paramedic to attempt to contact the parent, guardian, or legally authorized representative about the study. The paramedic self-report will also include a question about whether the parent expressed an objection to further data collection for the study for their child and whether they objected to the placement of the RR-EEG.

5.2 Data Collection During Hospitalization

5.2.1 Hospital Records

EMS and hospital records will be linked locally at each site based on patient identifiers including last name, first name, destination of transport, date of birth and date/time of ED arrival. Study data will be coded, so the patient's name is not transmitted to the DCC. The RC will collect ED-based data, disposition, and length of stay data from the hospital electronic records. The sample size is based on patients having a paramedic-witnessed seizure who are transported to EDs affiliated with the study. For patients transported to non-affiliated hospitals, the investigators will only attempt to gather EMS and paramedic self-report data.

5.2.2 Rapid Response EEG (RR-EEG) Data

To assess the primary outcome, a study team member or clinical personnel will apply the RR-EEG recording device to a sub-set of enrolled participants upon arrival at a study-affiliated ED, unless parent/guardian objection to participation has been received prior to or upon arrival. The RR-EEG will be placed, regardless of randomization status of the EMS agency, if the patient meets one or more of the following criteria:

1. The patient is actively having a seizure upon ED arrival, based on the parent/guardian, physician, or nurse's assessment OR
2. The patient is unresponsive to light touch or voice

These patients will have the device in place while unresponsive in the ED. The rapid response device records EEG data that are then uploaded to a cloud-based server. The device is synchronized to local time with settings that can be used to uniquely identify the site, so that the date/time stamp from the device can be used to link the EEG data for the study with a unique patient, based on their date/time of ED arrival at the study site. An epileptologist co-investigator will read the EEG waveform output to definitively assess the primary outcome, but this will not be done in real-time. The epileptologists

will be blinded to the clinical care that occurred in the ED when making their initial assessment of whether or not the patient was having a seizure on ED arrival. For patients who are 6–13 years old, 1 epileptologist will read approximately 90% of these RR-EEGs; however, approximately 10% of these RR-EEGs will be read by 2 epileptologists in order to determine inter-rater reliability. All RR-EEG output on study subjects <6 years old will be read by 2 epileptologists. If there is a discrepancy in the read between these 2 epileptologists, a third epileptologist will make a tie-breaking determination of the RR-EEG output.

The treating ED attending physician and triage nurse will also document whether the patient was having a seizure on ED arrival. A hierarchy of the preferred source of primary outcome assessment will be provided in the Statistical Analysis Plan.

6 Statistical Summary

6.1 Sample Size Justification

The frequency of seizures on ED arrival was estimated through simulation based on hypothesized frequencies for both conventional dosing and standardized dosing and based on prior data.[29, 31] The simulations used for calculating the sample size using the stepped wedge (SW) design accounted for the site-to-site variability in enrollment. Only randomization sequences that have an expected enrollment size for the conventional and standardized dosing arms within 5% of each other at the end of the trial will be considered. We expect to see 1,210 active pediatric seizure cases per year. Seizure cases that are observed during the SW transition periods are not counted towards either arm. Accounting for an 8% intra-cluster correlation, up to 10% lack of identification of eligible patients and exclusion of seizures during transition periods, we expect to see at least 820 seizure cases per year eligible for analyses. Based on this and the stepped wedge design as described above, we approximate 87% power to detect a difference in the rate of seizures on ED arrival rate between 39% in the conventional dosing arm and 29% in the standardized dosing arm in the 6 month – 13 year old patients.

6.2 Data Analyses

6.2.1 Study Outcomes

The primary outcome of seizures on ED arrival will be analyzed using a mixed logistic regression with a random effect for site. The main predictor of interest is arm (conventional weight-based vs. standardized age-based dosing). We will control for the logistic regression with appropriate covariates:

- Presence vs. absence of fever;
- New-onset seizure vs. previous history of seizures;
- Receipt of bystander-administered benzodiazepine prior to EMS arrival;
- Time (months) since study start;
- Sex;
- Age;
- Presence or absence of hypoglycemia (glucose <60 mg/dL).

The secondary outcomes (respiratory failure and time to first midazolam administration) and exploratory outcome (time to seizure cessation) will be analyzed in a similar framework as the primary outcome. For the exploratory measure of dose/route adherence with respect to these guidelines, we define adherence as receiving a first dose of EMS administered midazolam within 30% of the expected dose based on the protocol the paramedic is using at the time. Subjects will be considered adherent or non-adherent.

The study outcomes analyses will only include subjects who have not previously been in the study. Repeated events for the same subject will be identified by the identifiers used for record linkage, and only the initial event in the study will be included in the analyses of outcomes.

6.2.2 Subgroup Analyses

Subgroups of interest include:

- Method of dose determination
- Presence vs absence of fever
- New-onset seizure vs previous history of seizure
- Receipt of bystander-administered benzodiazepine prior to EMS arrival
- Route used to administer midazolam
- Sex
- Age
- Presence or absence of hypoglycemia
- Race/ethnicity

6.2.3 Safety Outcomes

Safety outcomes include:

- Life threatening hypotension
- Life threatening cardiac arrhythmia
- Depressed level of consciousness

These safety outcomes are defined in more detail in the 'Classification of Adverse Events' section. Life threatening hypotension and cardiac arrhythmia will be categorized as an occurred/not occurred event and will be compared between arms using a Mantel-Haenszel test, stratified by clinical center. Fisher's exact test will be used in cases of small counts. For depressed level of consciousness, Glasgow Coma Scores (GCS) will be assessed upon ED arrival and then regularly until departure from the ED and as needed to determine return to normal. We will compare return to normal between arms.

6.2.4 Safety and Effectiveness Interim Monitoring

The DCC will perform limited interim safety analysis at the end of each year of patient enrollment in order to prepare a report for the DSMB to determine whether or not the lower age limit for using standardized dosing can be de-escalated. The DCC will perform an interim safety analysis for the DSMB after 1.5 years of enrollment, comparing adverse events, including serious adverse events, between study arms using a Mantel-Haenszel test, stratified by clinical center and baseline severity

of symptoms. An interim safety and effectiveness analysis will be provided to the DSMB after 3 years, using Lan-DeMets spending functions corresponding to O'Brien-Fleming type boundaries.[8] Unlike a traditional randomized trial with approximately equal numbers of intervention and control patients throughout, the SW design results in more control patients at the beginning of enrollment and more intervention patients towards the end. Due to this, we will use Hemming, Lilford, and Girling's method to appropriately spend alpha.[14] No formal futility monitoring is anticipated.

6.2.5 Missing Data

Per the intention-to-treat principle, subjects who withdraw from the study or are lost to follow-up will have all available data used in the analysis. In the event that a substantial number of subjects are withdrawn or lost to follow-up, baseline characteristics and available information on hospital course will be reviewed and compared to subjects not withdrawn or lost, to assess empirically if these subjects differ from those remaining in the study for the scheduled treatment and follow-up time.

The outcomes are collected from the time period of prehospital care and the hospital stay, and will not require patient follow up beyond the hospital stay. Due to the ability to find the outcomes in the electronic health record, we anticipate very low missing rates for primary and secondary analyses. For this reason, the primary and secondary analyses will use complete case analyses if there are minimal missing data. If the rate of missing data is above an unreasonable threshold as defined in the Statistical Analysis Plan, we will perform multiple imputation using sequential regression methods to perform the analyses.

6.2.6 Population for Analyses

Patients transported to an ED that is not affiliated with the study will be analyzed separately for the limited primary, and safety outcomes that can be assessed. This will be used to demonstrate whether or not the patients who EMS transported to affiliated EDs had comparable outcomes to those they brought to non-affiliated EDs. Patients will be excluded from study analysis (primary, secondary, exploratory and safety) if they meet at least one of the following criteria, as reported by the bystander, determined by the paramedic, or noted in the hospital medical record:

- Presumed or known traumatic head injury within 24 hours of the seizure; OR
- Any prior history of psychogenic, non-epileptic seizures; OR
- Ventilator dependence at the time of the seizure; OR
- Intentional or unintentional ingestion of a medication or substance <24 hours prior to EMS care, if that medication or substance has the potential to cause seizures or altered mental status; OR
- Presence of absence seizures during EMS or ED care on the date of enrollment; OR
- Previously enrolled in the study.

7 Data Management

7.1 Clinical Site Data Management

Each clinical site will maintain study records in locked filing cabinets. The site will maintain an Essential Documents Binder, which may be in paper or electronic form.

7.2 Data Coordinating Center

7.2.1 Data Center Description

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for PECARN and a variety of other national research networks. Anchoring these services is a state-of-the-art, energy efficient data center. The data center facility supports more than 3500 users around the country and will provide a secure, reliable, enterprise-wide infrastructure for delivering mission critical DCC systems and services to PECARN.

7.2.2 Facility, Hardware, Storage, Data Backup and System Availability

The data center was built using industry standards and energy efficient cooling solutions. The data center is cooled by Liquid Cooling Package (LCP) inline cooling technology, providing the desired efficiency, redundancy and modularity. The LCP utilizes a hot/cold aisle design that allows for even air distribution to minimize hot spots. The data center's electrical power system contains an uninterruptible power supply with a diesel backup generator. The data center is protected with an FM-200 backed fire suppression system, which provides waterless fire suppression without leaving behind residue or particulate. Enhanced security measures are implemented to safeguard the equipment and the data within in it. Security measures are enforced 24 hours a day, seven days a week, 365 days a year by a combination of on-premise security guards, University police officers, and video surveillance.

The data center has a virtualized environment. This environment consists of more than 415 virtual servers across 25 host servers. Virtualization provides key advantages: (1) High availability – in the event of hardware failure, virtual machines automatically restart on healthy resources, minimizing impact to end-users; (2) Flexible infrastructure – compute and storage is seamlessly scaled as current needs change; (3) Rapid deployment – new resources are provisioned on-demand.

Production servers running mission critical applications are clustered and configured for failover events across multiple clusters. Entire servers are backed-up to a dedicated infrastructure. The backup repositories are encrypted-at-rest using AES-256. The storage area networking applications, clusters, and switch-to-switch links are highly redundant. Incremental backups of data occur Monday through Friday. A full data backup occurs weekly. Full backups are sent off-site on a weekly basis to a secure secondary location. The data center currently manages over 125 terabytes of data.

Information systems are available 24/7/365 unless a scheduled maintenance period or mitigation of an unexpected event is required. Critical systems availability has exceeded 99.9% for the past 5

years.

7.2.3 Security, Support, Encryption, and Confidentiality

The data center coordinates the network infrastructure and security with University Information Technology (UIT) at the University of Utah. This provides us with robust firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Centralized authentication and communication over public networks are encrypted using transport layer security (TLS) and/or virtual private network (VPN) technologies. Direct access to data center machines is only available while on premise or via a VPN client.

All network traffic is monitored for intrusion attempts. Security scans are regularly run against data center servers and IT staff are notified of intrusion alerts. Security is maintained with Windows user/group domain-level security. Users are required to change their passwords every 90 days. All files are protected at user/group levels and database security is handled in a similar manner with group-level access to databases, tables, and views. Finally, all laptops used by faculty and staff in the DCC are whole-disk encrypted.

The data center uses monitoring tools to continuously monitor applications and servers. Environmental and network systems are also monitored to ensure up-time. System Administrators are on-call 24/7/365 to respond to urgent events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems before access is provided.

7.3 Electronic Data Capture System

The Data Coordinating Center (DCC) will develop an electronic data capture system for this study. Data will be entered by each clinical site, and data quality will be monitored at the DCC. The DCC will use an electronic discrepancy management system to notify sites of inconsistent or erroneous data entry, which will be corrected by the clinical site. The discrepancy management system maintains an audit trail of all discrepancy resolution.

8 Study Site Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Study monitoring is critical to this process. Monitoring has been a very effective tool for maintaining data quality in previous PECARN studies, and we will utilize this process to ensure excellent quality data in the proposed study. The DCC utilizes risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Study monitors must be provided with appropriate access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

8.1 Site Monitoring Plan

A supplemental study-specific risk-based monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan may include the number of planned site visits, criteria for focused visits, additional visits or remote monitoring, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g., sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found.

8.2 Clinical Site Monitoring

Site monitoring visits may be conducted by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies.

8.3 Remote Monitoring

The DCC may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This may require uploading copies of medical records, patient study files, regulatory documentation, or other source documents for the monitor to review. Alternatively, other methods, such as remotely viewing source documentation, may be utilized. This helps assure protocol compliance and accurate data collection. The DCC may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

8.4 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection by representatives (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders or study sponsors, and the Institutional Review Board (IRB) of record (single IRB at the University of Utah). The investigative team will provide a summary of the efforts made to contact the parent, guardian, legally authorized representative and/or adult family members of the enrolled patients to the IRB at the time of continuing review.

9 Protection of Human Subjects

9.1 Risks to Human Subjects

9.1.1 Potential Risks of Patient Participation

This study involves more than minimal risk, since the intervention involves administration of a benzodiazepine, which has risk for respiratory depression. The intervention is a treatment for seizures, so there is risk that inadequately treated seizures will contribute to ongoing seizures, which could lead to brain damage and death. Since benzodiazepines are the standard of care for treatment of seizures in the EMS setting, the only alternatives are to vary the dose and the route of administration. Based on our prior work and other published literature, we believe that the proposed routes and doses that will be utilized in the intervention are the safest options for the study subjects.

We anticipate that there will not be an increased rate of adverse effects from our proposed standardized midazolam dosing relative to conventional dosing. Currently 50% of the participating EMS affiliates allow 10 mg of midazolam as a maximum dose for the IM/IN routes. In addition, this dose is similar to the standardized dosing used in the RAMPART trial.[32] In that study, 14% of patients required intubation, and there was no difference between those that received IM midazolam and those that received IV lorazepam. This is also similar to data from our preliminary studies on this topic.[29, 31] Thus, the proposed standardized dosing regimen is unlikely to increase respiratory failure risk relative to current practice.

There is minimal risk of potential loss of privacy and/or confidentiality, since personal identifiers will be gathered.

There are no psychological, social, cultural, financial or legal risks to the patient that are expected with standardized midazolam dosing relative to conventional midazolam dosing. There is a potential differential risk for ongoing seizures, recurrent seizures, hypoxia, and/or respiratory depression with one intervention relative to the other, though equipoise exists and is the premise for establishing these as the primary and secondary outcomes that are being evaluated for this study. This study involves no cost to the pediatric patients or their families. This study involves no cost to the EMS providers.

9.1.2 Potential Risks to EMS Providers

For the EMS providers, demographic information such as the EMS provider's years of experience, years of employment with the EMS system, and age will be collected to describe those who provided care to the study participants for subsequent peer-reviewed publication. Identifying information about individual providers will not be shared with anyone except study personnel, and their employers will not have access to study-related information about the care that the paramedics provided. Once again, secure data transfer and storage measures, as noted above, will be utilized for the EMS provider data. Information about the EMS providers, and all analyzed data, will be housed at the University of Utah Data Coordinating Center.

9.2 Adequacy of Protection Against Risks

9.2.1 Exception from Informed Consent (EFIC)

Administration of midazolam via the conventional and standardized protocols requires EFIC, since prehospital seizures are a potentially life-threatening, time-critical condition for which the standard of care is unsatisfactory, obtaining consent in the therapeutic window is not feasible, and there is a prospect of direct benefit for enrolled children. Although it is highly unlikely to be feasible, the investigators commit to: 1) Attempt to contact a parent, guardian, or legally authorized representative, for each patient within the therapeutic time window, if feasible, and ask for consent or, if not feasible, 2) Contact an adult family member within the therapeutic time window, if feasible, to ask whether the family member objects to the patient's participation. This will be accomplished by having the paramedic give the parent, guardian, legally authorized representative, or adult family member a phone number that will be accessible 24 hours per day, 7 days per week. At the time a parent/guardian phone call is received, the research staff will provide the study information contained in the parental notification form, answer questions about the study, and obtain verbal consent or objections to ongoing participation in the study, including the placement of the RR-EEG. If the parent, guardian, legally authorized representative, or other adult family member expresses a desire to discontinue participation, the date and time of objection will be noted, and the research staff will immediately stop all trial interventions and data collection. They will specifically communicate with the clinical staff in the affiliated ED to not place the RR-EEG, if it has not yet been placed, or to remove the RR-EEG, if it is already in place. If obtaining informed consent from the parent, guardian, or legally authorized representative is not feasible during the therapeutic time window and/or an adult family member cannot be reached during the therapeutic time window to object to trial participation, the research staff will, at the earliest feasible opportunity, inform the parent, guardian, legally authorized representative or adult family member about the patient's enrollment in the trial, provide details about the trial included in the parental notification/informed consent form, and inform the parent, guardian, legally authorized representative or adult family member that they may discontinue trial participation at any time. The patient will also be informed as soon as feasible and assent for continued trial participation will be obtained as appropriate.

The intervention is a system-wide implementation of a new protocol that will be applied to all patients transported by a participating EMS agency, so there is not an alternative option for the individual patient or the legally authorized representative.

The PediDOSE study meets the criteria for EFIC specified in FDA Regulation 21 CFR §50.24 for the following reasons:

- The human subjects are in a life-threatening situation that necessitates urgent intervention;
  - Ongoing seizures are life-threatening because they lead to respiratory depression, brain damage, and death.
- The therapeutic time window for treatment of convulsive status epilepticus with benzodiazepine medication is 0–5 minutes;[1]
- Available treatments are unproven or unsatisfactory;
  - Currently 1/3 of these patients arrive at EDs still having a seizure, so conventional treatment and dosing is unsatisfactory.

- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention;
  - It is unknown if standardized dosing is more (or less) effective than conventional dosing, and the impact on safety is unknown.
- Obtaining informed consent prior to seizure management in the field is not feasible because the therapeutic window is too short and many pediatric seizures in EMS are new-onset in nature, making it impossible to predict in advance who will be eligible for the study;
  - The on-scene paramedic(s) will be focused on high priority patient care steps (e.g., patient assessment, intervening for respiratory distress, determination of the midazolam dose required to stop the seizure, drawing up the medication for administration, reassessing the patient);
  - Parents/guardians may be absent; if they are present, they are often in distress when their child is having a seizure.
- The intervention must be administered before consent can be obtained;
  - Since untreated seizures can lead to self-sustaining status epilepticus,[23, 34] it is imperative that treatment is not delayed.
- There is no reasonable way to identify prospectively individuals likely to become eligible for participation;
  - Many children who have a seizure in the EMS setting experience it for the first time in their lives, making prospective identification impossible.
- Participation in the research holds out the prospect of direct benefit to the subjects;
  - Since prior research demonstrates that midazolam 0.2 mg/kg given IN or IM is efficacious at stopping seizures, participation in this research study in which the intervention is focused on optimizing delivery of midazolam at this dose and via one of these routes does hold the prospect of direct benefit to the subjects.
- The clinical investigation could not practicably be carried out without the waiver.

Therapeutic Time Window. Kaplan-Meier curves from an EMS-based study demonstrate the biggest reduction in duration of status epilepticus in patients treated in the first 0–5 minutes.[1] Another EMS-based study of status epilepticus showed that among subjects whose seizures ceased before arrival to the emergency department(ED), the median time to active treatment was <5 minutes.[32] Specifically in pediatrics, treatment delays in seizures lasting more than 5 minutes are associated with prolonged status epilepticus,[9] such that many hospital-based guidelines specifically recommend the administration of first-line benzodiazepine treatment within 5 minutes.[35] This is also consistent with Canadian guidelines on the emergency management of convulsive status epilepticus in pediatric patients, which allows for 5 minutes to establish that a seizure warrants treatment, 5 minutes for the first benzodiazepine dose to be administered, and another 5 minutes for a second benzodiazepine dose to be administered for ongoing seizures.[24]

Community Consultation. Each site will prepare a community consultation plan, will submit that plan to the University of Utah IRB for approval, will execute the community consultation, and will provide the results of that consultation to the Utah IRB for approval by the IRB. The community consultation plans will include public disclosures, opportunities to obtain information

about the study, informational materials for distribution, and local input from the community using an anonymous survey and semi-structured interviews with members of the community, including parents or guardians of children in the eligible age range for the study. These strategies will also be used to gather feedback from paramedics in these communities. As part of the community consultation process, the public will also be informed about the options they will have to object to further participation in the trial if an ambulance is called for a seizure in a pediatric family member. Each site will have its own individualized consultation plan to meet the needs of its specific community. Large, open public forums will likely not be planned, since the COVID-19 pandemic is still ongoing and community participation in such events may be unsafe for the public. Furthermore, such forums have had limited success in previous PECARN network studies requiring EFIC.[4, 5, 18, 27]

9.2.2 Opt Out, Notification, and Withdrawal

Opt-out. Since EMS medical directors will change EMS agency protocols to standardize and ensure safe care, individuals cannot meaningfully opt out of the study intervention itself, which is the revised EMS seizure protocol that utilizes age-based midazolam dosing. However, paramedics will be informed about options available to participants to object to the collection of study data and will be provided with a contact phone number that can be given to parents in the event there is an opportunity for research staff to discuss study information with the parent/guardian/other in the pre-hospital environment. If the adult in attendance with the child at the time of enrollment tells the paramedic that they object to participation in the trial, the paramedic will convey that information to the research staff after arrival to the ED as well as the date/time of the objection. This information will be collected as a part of the paramedic self-report, so that study-related data collection is halted from the date/time that the paramedic received notification of the objection.

Since this is a study involving only children, the research coordinator (RC) at each site will notify the parent or guardian of the child and specific study patients (defined on the following page) about enrollment in the study at the earliest feasible opportunity. This notification will involve a description about the study, including a notification form describing options for continued study participation. This form provides options for ongoing participation. These options are:

1. I agree to continued participation in the study, including data collection regarding care that my child receives until he/she is discharged from the hospital
2. I object to continued participation in the study, including no further trial interventions, the use of the rapid response encephalogram (RR-EEG), and no additional data collection
3. I object to continued participation in the study including no further trial interventions, but allow ongoing/additional data collection

If the RC cannot successfully notify the parent, guardian, legally authorized representative in-person or via phone, then the RC will notify another adult family member or responsible adult in attendance with the child. If no one is in attendance with the child or if the child has already been discharged before the RC can make in-person contact in the hospital, the RC will attempt to notify the parent/guardian via phone. If that is unsuccessful, the RC will notify the parent/guardian via mail.

The majority of the children having a seizure in each of the participating metropolitan areas are

transported to children's hospital EDs that are affiliated with the study and that have RC staffing. Since there are numerous other EDs in each of these metropolitan areas, most of these EDs do not have any RC staffing, and the number of RCs required to staff all of these EDs would likely exceed the number of potentially eligible patients who could be enrolled at these other EDs, it is not practicable to provide in-person notification in situations when the patient is transported to these non-affiliated EDs. Therefore, RCs will make attempts to notify the parent/guardian of these patients by phone and will then notify by mail if phone contact is unsuccessful.

Earliest Feasible Opportunity. The earliest feasible opportunity for notification of study enrollment occurs in the Emergency Department and research staff will work closely with hospital staff to ensure the parents are notified at the earlies opportunity.

At the earliest feasible opportunity to communicate with the patient, the RC will also give an opportunity for certain minors to object to further participation if they are:

1. 7–13 years old and
2. Have the developmental ability to communicate and
3. Do not have a baseline significant cognitive impairment noted in their medical record that would impair their ability to comprehend information about the trial

Patients who are 6 months to 6 years old will not be informed about the trial, since they have not yet attained the appropriate cognitive development to comprehend information about the trial.

If the earliest feasible opportunity occurs when a RC is not present in the hospital, typically in the middle of the night, clinical staff at affiliated hospitals may provide the parent with written information and a phone number where questions can be answered. If the patient is transported to a non-affiliated ED where no study-affiliated RC is present at all, the RC will make attempts to notify a parent/guardian by phone at the earliest feasible opportunity. If attempts to contact by phone are unsuccessful, the RC will send appropriate notification forms via mail and/or email.

In the event that the research subject dies before notification occurs, the research staff will send a letter to the parent/guardian 1–2 weeks after the subject dies. The reason for waiting at least 1 week is that the family will be too distraught to process this information soon after the death occurred.

Withdrawn Participants. Once notification of objection is received by the study team, no further data collection or study interventions, including use of the RR–EEG will be attempted in accordance with the option selected at the time of signature or verbal notification. As per the FDA guidance regarding withdrawn participants, data that has already been collected will be retained in sufficient manner to maintain adequate case histories recording all observations and other pertinent data to the investigation on each individual treated with the investigational product.

Public Disclosure of Trial Results. The investigators will disclose information about the study's procedures, risks, and benefits prior to initiation of the study (as part of community consultation) and will publicly disclose the study findings after completion. This disclosure may occur through

television and radio public service announcements, newspaper articles, posted flyers in pediatric EDs, pediatric neurology clinics, and general pediatrics offices, via the study website, and/or through presentations to professional organizations. Physically posted and mailed information will be in English and Spanish.

9.2.3 Collection of Mortality and Outcome Data on All Eligible Subjects

Since the unit of randomization is the EMS agency, failure to collect outcome and safety data on all patients treated with the EMS seizure protocol and transported to the study hospitals would lead to incomplete and potentially biased data collection that would inaccurately assess the effectiveness and safety of the system-wide protocol implementation. Patients who meet the following criteria are considered to be research subjects in this study:

1. Ages 6 months to 13 years old and
2. Have an active seizure in the presence of a paramedic in one of the EMS agencies participating in the study

Since all of these patients are either in the intervention (treated under the revised EMS seizure protocol) or control group (treated under the existing EMS seizure protocol), all of the patients who meet the above noted criteria will be enrolled in the study under EFIC. The scientific validity of the study is dependent on capturing all eligible patients during the study period, as one of the major goals is to accurately describe the characteristics of the entire eligible population.

Since all patients who meet the above-noted criteria will be exposed to either the intervention or the comparison, the investigators will attempt to do all of the following with parents, guardians, legally authorized representatives, or another adult family member of patients who meet the above-noted criteria: 1) Obtain informed consent, if feasible, as noted in Section 9.2.1 on page 26; 2) Notify them within the therapeutic time window as noted in Section 9.2.2 on page 28; and 3) Provide notification to them at the earliest feasible opportunity as noted in Sections 9.2.1 on page 26 and 9.2.2 on page 28; and 4) Provide an opportunity to object to further data collection as noted in Sections 9.2.1 on page 26 and 9.2.2 on page 28.

Since it is important to ensure that there is no discrepancy in safety between patients transported to the affiliated EDs and those who are taken to other non-affiliated EDs, it is scientifically essential to acquire data on mortality for all patients involved in the study. In addition, we plan to collect data on the primary outcome (having a seizure on ED arrival) based on the paramedic self-report and documentation in the EMS record, as long as the paramedic has not been notified of any objection to collection of this information and the research staff has made their best efforts to provide notification.

This study utilizes a stepped-wedge design, and the patients who are being treated under the EMS agency's existing seizure protocol (prior to randomization to implement the intervention—the standardized seizure protocol) are enrolled in the control group. Since comparing the intervention group to the control group is essential to the scientific design of the trial, we will collect data on patients in the control group who are transported by the participating EMS agency. For patients between 6 months and 23 months old, they will receive care under the EMS agency's existing

conventional dosing seizure protocol until the Data Safety Monitoring Board (DSMB) deems that it is safe to lower the age for standardized dosing. These patients will be enrolled in the control group until that happens. Since comparing the intervention group to the control group is essential to the scientific design of the trial, data will be collected for these control group patients until the DSMB deems that it is safe to make them part of the intervention group.

9.2.4 Vulnerable Subjects

Vulnerable populations in this study are children, including Wards of the State, and employees of EMS agencies. Children will be included because this is a study that focuses on improving pediatric seizure management in EMS. Wards of the State are included in the study because there is no way to exclude participants who receive EMS treatment based on custody status. The rationale for including children in a study like this is that children as a whole receive care that is not equitable relative to adults in the EMS setting, and pediatric seizures in EMS have been identified as a high priority area of research due to their frequency and the gaps in knowledge that exist.[2, 10, 17] There is no undue coercion since care received in the prehospital setting and the emergency department will be administered according to existing patient care protocols/guidelines. Research in children involves special protections under 45 CFR §46 Subpart D "Additional DHHS protections for children involved as subjects in research" and 21 CFR §50 and §56. The study in this protocol is permissible under these regulations as:

- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR §46.405).

Wards of the State enrolled in this study will be afforded the same rights and protections as all other subjects enrolled in the study as outlined in section 9.2.1. Permission from a legal guardian or legally authorized representative will be sought. Any data collected up until the time of withdrawal will be retained.

EMS providers are potentially vulnerable because data will be collected that could potentially identify individual practice patterns for paramedics administering care under this protocol. This risk is mitigated by the employment of confidentiality practices. Identifying information about individual providers will not be shared with anyone except study personnel, and their employers will not have access to study-related information about the care that the paramedics provided.

9.2.5 Institutional Review Board and Human Research Protection

The Institutional Review Board (IRB) at the University of Utah will serve as the single IRB. The Utah IRB has extensive experience with single IRB implementation due to our participation in the NCATS funded Trial Innovation Center, which has implemented over 35 sIRB studies, several with EFIC.

In addition to sIRB activities, each institution has Human Research Protection activities that will be completed prior to site activation. These include conflict of interest, assuring competence of investigators, impact on hospital services, etc., and are individualized to each site.

9.2.6 Protections Against Risk

Expertise of providers. Children eligible for this study are cared for by expert pre-hospital paramedic staff, and are taken to emergency departments that are staffed by qualified pediatric emergency physicians , nurses and respiratory therapists. Subjects are evaluated continuously in the emergency setting, and all centers are well prepared to evaluate and treat any complications that can arise from participation in the study.

Loss of Confidentiality The minimal risk of loss of privacy is mitigated by the substantial data management resources and security described in Section 7.2.3 on page 23.

9.3 Potential Benefits of Proposed Research

Potential benefits for subjects who are treated with standardized, age-based midazolam dosing include: few medication dosing errors, faster resolution of their seizure, less respiratory failure, and decreased length of hospital stay. These benefits are theoretical, since clinical equipoise exists and it is unknown if standardized, age-based midazolam dosing is better than conventional dosing with respect to these outcomes. The results of this study will give valuable feedback to the EMS system regarding prehospital seizure treatment for pediatric patients. The information from this study could be used to improve the care of children in the prehospital setting. The anticipated benefit to society in understanding how to optimally dose seizure medication for children in the prehospital setting outweighs the minimal risk of loss of confidentiality.

9.4 Importance of the Knowledge to be Gained

The importance of the knowledge to be gained from this study is that current treatment of pediatric seizures in EMS has a high failure rate, but doing this study will demonstrate if utilizing age–based, standardized midazolam dosing improves outcomes. If outcomes are improved, the findings from this study could be easily translated into practice in numerous EMS agencies across the country. Thus, this study has the potential to positively impact the management of pediatric seizures on a national level. If this study demonstrates that standardized age-based dosing is more effective than conventional dosing, it will shift the paradigm in EMS management of pediatric seizures across the country.

10 Data and Safety Monitoring Plan

10.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB) composed of individuals independent of the study. Members will have expertise in statistics, medical ethics, emergency medical services, pediatric emergency medicine, and/or neurology. The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim data as applicable. The purpose of the DSMB is to advise the Principal Investigator(s) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance

of individual agency and site, review of adverse events, and other subject safety issues.

10.2 Adverse Event Reporting

Adverse events occurring in the field or hospital will be recorded for eligible subjects, up to the time of ED discharge, hospital discharge, or 12 hours after ED arrival, whichever is earliest.

10.2.1 Definition of Adverse Event and Serious Adverse Event

Adverse Event (AE). An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR §312.32 (a)). An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom.

Serious Adverse Event (SAE). A serious adverse event (SAE) for this population is an adverse event that:

- results in death; or
- is life-threatening (immediate danger of death from the event as it occurred); or
- requires new inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

10.2.2 Classification of Adverse Events (Relatedness and Expectedness

Clinical judgment is required for properly classifying relatedness and expectedness for adverse events. It is not appropriate to classify an event as possibly related if, in the opinion of the clinical investigator, it is clinically unlikely that the event is related. It is impossible to prove a negative, and the FDA expects clinical judgment to be used in assessing relatedness. Similarly, it is not appropriate to classify an event as unexpected because the patient was not anticipated to suffer the event at the time of enrollment into the study, if the event is a known sequelae of the underlying disease process or has been previously noted with midazolam administration.

Relatedness: The suspected relationship between midazolam administration and any adverse event will be determined by the site investigator using the criteria below. *Relatedness must be assessed by an investigator and may **not** be assessed by a research coordinator.*

Not Related: The event is believed to be related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows a clinically compatible temporal sequence from the time of administration of midazolam, but could have been produced by other factors such as the

subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of midazolam administration, and *cannot be reasonably explained* by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with complications of seizures, existing conditions for the patient, nor consistent with adverse events noted from midazolam administration.

Expected: An event is considered expected if it is known to be associated with the underlying condition or is related to midazolam administration. An event may be expected despite the study subject's clinical state immediately prior to the event.

Unexpected: An event is considered unexpected if there are no prior data linking this event with either the patient's condition or administration of midazolam.

Adverse events that are expected from the intervention include dizziness, hiccups, and nystagmus. Additional adverse events that will be closely monitored are the presence of anterograde amnesia, nausea, vomiting, hypoglycemia, headache, syncope, abnormal movements (tremors/twitches not due to a seizure), agitation, cellulitis or abscess at the IM injection site, rash at the IM injection site, hematoma at the IM injection site, epistaxis, or hypothermia (temperature <35° C). We do not anticipate an increased risk of these complications by giving midazolam using standardized, age-based dosing relative to conventional dosing.

We plan to monitor for these as well as the following critical adverse events, which are safety events of special interest:

- Life threatening hypotension unresponsive to 20 ml/kg fluid bolus: systolic blood pressure remaining below age-specified thresholds in mm Hg:
  - 6–11 months: < 60
  - 1–10 years: < [(age in years) x 2] + 70
  - >11 years: < 90
- Life threatening cardiac arrhythmia requiring intervention with chest compressions, pacing, defibrillation, or the use of an anti-arrhythmic agent or procedure;
- Respiratory failure in the prehospital setting or within 30 minutes of ED arrival, requiring bag valve mask (BVM) ventilation, bi-level positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), or placement of a supraglottic airway (SGA) or endotracheal intubation (ETI);
- Depressed level of consciousness defined as Glasgow Coma Score <8 that persists more than 4 hours after ED arrival.

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Medical or surgical procedure
- Concomitant medication: started, changed, or discontinued
- Other, specify
- No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with sequelae
- Symptoms persist

10.2.3 Data Collection Procedures for Adverse Events

All adverse events (including serious adverse events) in the reporting window will be recorded according to relatedness, severity, and expectedness, as well as their duration and any treatment prescribed.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center.

10.2.4 Unanticipated Problems (UP)

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related or possibly to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event. After receipt of the complete report, the Data Coordinating Center will report these unanticipated problems to the NINDS Project Officer in an expedited manner (as close to 24 hours as possible). The medical monitor (Section 10.2.5 on the next page) for the study will assess the report, and reporting to the University of Utah IRB, acting as the single IRB for the study, may be required. In addition, dependent on the nature of the unanticipated problem, all participating institutions may require notification. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NINDS staff cannot be reached expeditiously, the Data Coordinating Center will notify the study investigators (Dr. Shah) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NINDS staff after discussion with the DSMB.

10.2.5 Monitoring Serious Adverse Events

A qualified physician will be designated to fulfill the function of the medical monitor for this study. Site investigators and/or research coordinators will report serious adverse events to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign off on each SAE report after review. All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by DSMB members and NINDS staff. The SAE reporting process may be incorporated into the Electronic Data Capture (EDC) System in use for the study.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NINDS staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the NINDS staff and the DSMB chairperson cannot be reached expeditiously, the Data Coordinating Center will notify the study investigators (Dr. Shah) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NINDS staff after discussion with the DSMB. The sIRB in Utah will be notified, and each site investigator will notify their institutional Human Research Protection program of the trial suspension.

After notification of the NINDS Program Official or Project Officer, and the DSMB chairperson, of *serious, unexpected, and study-related* adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigators (Dr. Shah) and all clinical investigators, who will be instructed to report this to their institutional Human Research Protection program.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

10.2.6 Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the affiliated hospital, will be followed by the site investigators until the events are resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized, and continuity of care with a responsible clinical team has been assured.

10.2.7 Reporting to the Food and Drug Administration

Serious, unexpected and related adverse events will be reported to the FDA in an expedited manner consistent with FDA requirements. The Data Coordinating Center will prepare the report for

submission by the principal investigator, Dr. Shah, who will hold the IND.

11 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A subset of research and/or clinical staff will also receive training on the RR-EEG device directly from the device manufacturer's representative, so that they can train other relevant site staff on the proper storage, application, use, and disposal of the device. No site will be activated until all training requirements have been fulfilled by the site investigators and research staff.

A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the study PI (Dr. Shah), will be the main contact for study questions.

All paramedics in the participating EMS agencies will be informed about the details of the study before any patient enrollment begins, so that they are aware of the study and know how to notify research staff at the hospital if an adult family member of the patient informs them of their desire not to have the patient's data utilized for the study. In addition, mandatory in-person training of EMS providers, will occur once for each paramedic in a given EMS system and begin no earlier than 4 months prior to implementation of the standardized protocol. The number of trainings in each EMS system will be determined based on EMS system logistics to ensure that all providers can attend the training once. When the new standardized dosing protocol is implemented, all adults and children will be treated with the protocol because the EMS agencies have agreed to change their system-wide seizure protocol for the study. Standardization of the protocol is necessary to avoid confusion among paramedics when treating patients in the field.

12 Regulatory Considerations

12.1 Food and Drug Administration

While midazolam is approved for use in pediatric patients by the FDA, and there are several FDA approved EEG recording devices that can be used in children, this study is being done under Exception from Informed Consent (EFIC). For that reason, an IND has been submitted to cover the drug (IND 156119).

The FDA has determined that an IDE is not required for this trial, since this study will not investigate a new or modified use of the RR-EEG device, nor will safety or effectiveness data for the device be collected. No site is required to use the RR-EEG device for clinical decision-making. If a site chooses to use the RR-EEG device as an adjunct to clinical decision-making, they will be advised of the age-specific FDA approval for different features of the device.

All IRB-approved community consultation and public disclosure materials will be submitted to the FDA and to Public Docket number 95S-0158.

12.2 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

12.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

12.4 Clinical Trial Registration Requirements

The PediDOSE trial is registered at https://clinicaltrials.gov in accordance with Federal regulations (ClinicalTrials.gov ID: NCT05121324).

12.5 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

12.6 Public Use Data Set

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect

interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

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