

**Treating Respiratory Emergencies in Children Study
(T-RECS)
PECARN Protocol Number 055**

Pediatric Emergency Care Applied Research Network
National Heart, Lung, and Blood Institute (NHLBI)

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Treating Respiratory Emergencies in Children Study

Short Title: T-RECS

PECARN Protocol Number: 055

Lead Investigator and Author:

Matthew Hansen, M.D

Oregon Health & Science University

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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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1 Study Summary

Severe acute asthma is the most common pediatric medical emergency in children. 1 in every 250 deaths worldwide are due to asthma.¹ Over 200,000 children have a 911 EMS activation for respiratory distress each year, most of whom have acute wheezing. A study by Nassif et al conducted in Houston, Texas found that when children require a 911 EMS activation for acute wheezing and have respiratory distress defined as an abnormal respiratory rate, 82% require admission to an intermediate or ICU level of care. Wheezing is a symptom that includes multiple phenotypes, but is the most common respiratory symptom requiring prehospital treatment in children. Paramedics are not trained to diagnose illnesses but respond to specific signs and symptoms using a specific treatment protocol. Early treatment of wheezing children in the prehospital setting could more rapidly relieve respiratory distress symptoms, prevent hypoxia, reduce invasive interventions, and reduce the need to be hospitalized, thereby facilitating earlier return to normal daily activities. Pilot data from one site found that hospital admission was reduced from 30% to 21% among children when a pediatric asthma protocol with oral dexamethasone was implemented in an EMS system. This same study showed that among children with respiratory distress, the ICU/intermediate care admission rate decreased from 82% to 44% after implementing the protocol change. The EMS system in this study has a two-tiered response which may have inflated these estimates specifically among children with respiratory distress compared to other systems, and intermediate-care admission criteria likely vary between hospitals. Beyond this single retrospective quasi-experimental study, there is limited additional evidence on whether inhaled ipratropium and orally administered dexamethasone given in the prehospital setting reduce hospital admission rates compared to administration after arrival to the ED, where they are the standard of care and have proven benefit.

Respiratory distress from wheezing in children over two years of age is a common time-sensitive problem with simple, effective, and low-risk treatments. Prehospital care is generally directed by specific treatment protocols. A recent review of EMS protocols for the 30 largest US metro areas identified wide variability in treatment for wheezing children. All protocols included albuterol administration, though only 25% of agencies included inhaled ipratropium. Some agencies include corticosteroid treatment, though the most common is intravenous methylprednisolone, which is rarely used in children. Only 10% of agencies included oral dexamethasone, which is the most feasible for children in EMS since it does not require a needle poke. Beyond the limitations of what protocols allow prehospital providers to give, we found a substantial portion of children do not receive prehospital albuterol, ipratropium, or dexamethasone in agencies that include these medications in their protocols. This is likely due to limited training and overall discomfort with giving children medication. There is currently little prehospital data regarding the effectiveness of most interventions for pediatric emergencies and little understanding of how to prioritize the relatively scarce pediatric EMS training and operational resources. A clinical trial is critically needed to evaluate if patient outcomes can be improved by allocating EMS resources to the implementation of interventions for children with life-threatening wheezing that have a proven benefit in the ED.

Our long-term goal is to conduct a randomized trial using a hybrid stepped-wedge design to evaluate an evidence-based EMS protocol for children with a 911 call for life-threatening wheezing/asthma. The specific health outcome is the hospital admission rate. The study population is children aged

2–17 with life-threatening respiratory distress from acute wheezing/asthma. This pilot study is preparatory to a future larger trial. The overall objective of this pilot study is to address specific questions related to the implementation of the study and ensure its feasibility. The study will be conducted in the Pediatric Emergency Care Applied Research Network (PECARN) EMS Affiliates (EMSAs). The PECARN network is needed because of its existing and proven pediatric research infrastructure and its multiple EMS agencies, ensuring sufficient patient enrollment to reach a generalizable conclusion. We will address study feasibility through the following specific aims.

1.1 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. To develop and produce a prehospital checklist for the treatment bundle, including ipratropium and dexamethasone. We will 1) finalize the checklist by consulting agency medical directors and 2) verify the format and structure of the checklist using PECARN EMS advisory committees and/or EMS providers.

Specific Aim 2. To determine the feasibility of collecting patient outcomes for children with life-threatening wheezing/asthma treated in the EMS system. We will conduct a pilot study of the treatment bundle and evaluate the hospital admission rate, the NIH PROMIS asthma impact scale, the ICU admission rate, and other clinical outcomes at both PECARN-affiliated and community hospitals where patients are transported by EMS.

Specific Aim 3. To evaluate the implementation of the EMS treatment bundle and checklist using the RE-AIM framework. We will survey EMS agencies and obtain feedback from practicing EMS providers using the T-RECS EMS operations committee and/or consultation with practicing EMS providers to evaluate checklist implementation.

1.2 Hypotheses

1. We will collect hospital admission status from 80% of patients and NIH PROMIS asthma impact scale scores from 60%.
2. EMS providers will find the checklist and protocol acceptable and feasible to implement.

This study will provide the necessary data to ensure the eventual trial is feasible, primarily by establishing the ability to measure the outcomes of interest and evaluating implementation. This study is innovative by focusing on pediatric care in the prehospital environment, a critical component of our emergency care system often not included in research.

2 Rationale and Background

Several specific items need to be addressed in order to meet the objective of addressing feasibility and implementation obstacles before the larger trial (Table 1). We expect the clinical treatment protocol will be acceptable to EMS agencies. Our team has extensive pediatric EMS operational experience, and many team members work with EMS agencies to implement pediatric treatment protocols. Furthermore, the National Association of State EMS Officials (NASEMSO) treatment protocol has previously been implemented in Houston and Portland. However, gaps remain in fully applying the protocol to all patients who could benefit. For example, in Houston and Portland, less than 25% and 33% of eligible patients are treated with systemic corticosteroids, respectively. Because of this, we will develop a checklist to aid in improving adherence to the treatment protocol. Checklists are effective at improving quality of care and protocol adherence in studies of adults in EMS.¹⁻³ These studies typically find an absolute 10–20% improvement in protocol adherence with the adoption of a checklist. This is a modest effect and results in protocol adherence ranging from 35–65%. Though this is not what would typically be considered good protocol implementation from a hospital-based perspective, practice variation is a reality of EMS care and is an important reason why we are proposing a pragmatic trial.

We also need to understand the feasibility of collecting the outcomes of interest, in particular the NIH PROMIS asthma impact as a potential key secondary outcome of the larger study. Patient-reported outcomes have not been applied to EMS research before, and the feasibility of collecting this outcome is unclear and a vital component of this pilot study. Finally, we will evaluate the implementation of the treatment protocol using the RE-AIM framework.⁴

Table 1: Specific Aims and Outcomes for Each Aim

Aim	Approach	Study Sites	Outcome/Milestones
Aim 1	Develop an implementation plan for the checklist for treatment protocol	All 9 PECARN EMSAs and field advisory committees	Agreement on the checklist content and format by all sites
Aim 2	Evaluate the feasibility of collecting outcomes	Salt Lake City, Buffalo, Charlotte	Collection rates of: Hospital admission status, NIH PROMIS asthma impact, critical care interventions
Aim 3	Evaluate protocol implementation (RE-AIM)	Salt Lake City, Buffalo, Charlotte	Rates of protocol application by providers to patients

2.1 Significance

Children with life-threatening wheezing/asthma are commonly cared for by EMS providers.

Respiratory disorders are among the highest contributors to pediatric morbidity and mortality and are the most common reason for hospitalization in the US. Approximately 2 million children are transported by EMS each year in the US, and respiratory distress is the most common medical complaint requiring prehospital treatment with at least 200,000 transports per year.⁵ Acute wheezing

is the most common cause of respiratory distress in the prehospital setting.⁶ However, the impact of prehospital interventions for pediatric wheezing is unclear though it has high public health significance.⁷ Children who arrive by EMS to an ED have five times the odds of being critically ill and nearly three times the odds of requiring hospitalization than those who arrive by other means.⁸ Also, children who arrive by EMS are more likely to be African American, publicly insured, and live in urban areas.⁸ These factors are associated with poor asthma control and more severe symptoms.^{9–11} Prehospital treatment is likely to impact severely ill and vulnerable patients.

Children with life-threatening wheezing could significantly benefit from more aggressive prehospital stabilization. Early aggressive treatment in the prehospital setting could more rapidly relieve wheezing and respiratory distress, prevent hypoxia, reduce intensive/invasive interventions, and reduce the need to be hospitalized, facilitating earlier return to school and other daily activities. Pilot data from one site found that hospital admission decreased from 30% to 21%, and critical care admissions decreased 30% among children when paramedics were permitted to use oral dexamethasone to treat wheezing children.¹² An ED-based study found that when triage-nurses initiated steroids, the steroids were given 44 minutes sooner, and the hospital admission rate decreased from 19 to 12%.¹³ A 2001 Cochrane review also found that steroids administered in the first hour of an ED visit reduce the odds of admission by nearly half.¹⁴ However, the prehospital data comes from a single site before-and-after study. It is necessary to verify these results in a larger trial to justify the resources required by EMS agencies to change their practice.

Prehospital care is highly protocolized when compared to ED or hospital care. In preparation for the study, we reviewed EMS protocols for the 30 largest US metro areas and found wide variability in treatment for wheezing children. All protocols included albuterol administration, but only 25% of agencies allow ipratropium. Though some agencies allow corticosteroids, most can only be given IV. Only 10% of agencies include dexamethasone, which is easier to administer since it can be given orally, IM, and IV and therefore is more feasible to use in children during prehospital care. Additionally, 30% of wheezing children do not receive prehospital albuterol, and relatively few potentially eligible children receive ipratropium (25–30%) or corticosteroids (10–33%) in EMS agencies with protocols that include these medications.^{12, 14, 15} There is currently little data regarding the benefits or harms of most prehospital interventions for pediatric emergencies and little understanding of how to prioritize pediatric EMS training and operational resources to maximize patient outcomes. Therefore, a clinical trial is needed to evaluate whether expanded prehospital interventions for children with life-threatening wheezing/asthma will result in improved patient outcomes.

The majority of US EMS agencies use albuterol for wheezing, so the study treatment bundle will primarily change existing care protocols by adding inhaled ipratropium and dexamethasone. There is substantial evidence from ED trials that both of these medications independently improve outcomes, primarily by reducing the rate of hospital admission for wheezing children.^{16–19} In particular, corticosteroids given by mouth early in the ED course are associated with reduced hospitalization rates in children with wheezing, typically reducing odds of admission by 50%.^{13, 18, 19} However, it is unclear if these same treatments applied in the EMS environment to children with life-threatening wheezing will have the same benefits. One reason that these treatments may not change outcomes when given in the EMS environment is that not enough time is gained relative

to when the medications are being given in the ED. It is also possible that the treatments are not given to the correct patients, or that paramedics may not follow the protocol as directed. In general, EMS protocol adherence across all ages and diseases is low to moderate (20–65%), which is a systemic problem in EMS and beyond the scope of this study.^{12,20,21} To address this, we will optimize protocol adherence while maintaining a pragmatic and efficient study design to ensure the generalizability of the results in the US EMS system. Also, paramedics are not trained to diagnose diseases but respond to signs and symptoms. These factors, coupled with limited pediatric training and exposure, are additional potential systemic challenges to the effectiveness of new pediatric treatments in the prehospital setting. Therefore, there is a critical need for a pragmatic clinical trial to evaluate the effectiveness of ipratropium and dexamethasone in the prehospital environment for children with life-threatening wheezing/asthma.

2.2 Innovation

Pediatric Prehospital Research is Innovative.

There is currently no prospective data from the EMS environment to guide the treatment of children with acute life-threatening wheezing despite this being one of the most common reasons for a pediatric 911 call for serious pediatric illnesses encountered by EMS. The EMS system is the leading edge of the healthcare system for some of the most vulnerable patients but lacks strong evidence for most areas of practice. EMS research that includes pediatric patients is innovative since the small number of EMS-based trials have focused on the care of adults.

We will use a “Hybrid 1” mixed clinical-implementation design.

Prehospital care is based on signs and symptoms and is highly protocol-driven. In contrast, hospital-based ED care relies on more specific assessment and diagnosis before initiating treatment, which may follow a guideline or clinician judgment. Given the importance of protocols in EMS, an intervention’s success is significantly impacted by its implementation. Protocols are often developed in the abstract and then broadly implemented in the real world. In this pilot study, we will use the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework to evaluate the clinical treatment bundle and checklist implementation.⁴ Thus, we will use this “real world” pilot study to collect key implementation data that will impact how the intervention is deployed in the full trial. We will use the “Hybrid Type 1” clinical-implementation design as described by Curran et al.²² In this design, an effectiveness study (in this case, a pilot) is modified to achieve a secondary goal of studying implementation. Our primary goal is to evaluate the feasibility of collecting the outcomes of interest. We will also collect key data related to the implementation of the clinical care protocol and checklist that will create a framework to optimize the intervention in the full trial. This “Hybrid Type 1” study is innovative in the EMS environment and has many potential benefits in this unique care setting.

3 Subject Eligibility, Accrual and Study Duration

3.1 Eligibility Criteria

Eligible participants will be identified by on-site study staff.

Inclusion criteria are:

1. Ages 2–17 years; AND
2. Transported by EMS through 911 activation; AND
3. Prior history of wheeze/asthma, current asthma symptoms (dyspnea or wheeze); AND
4. At least 4 of the following:
 - Visible use of accessory muscles/retractions
 - Inspiratory and expiratory wheezing or silent chest
 - Abnormal RR for age
 - For < 6 years ≥ 46 breaths/min
 - For ≥ 6 years ≥ 36 breaths/min
 - Agitation, drowsiness, or confusion
 - Oxygen saturation < 93% on room air

Exclusion criteria are:

1. History of albuterol, ipratropium, or dexamethasone allergy
2. Known or suspected pregnancy
3. Prisoner
4. Croup
5. Suspected airway foreign body
6. Respiratory distress not due to bronchospasm/wheeze
7. Parent, legally authorized representative (LAR), subject, and/or family member objects to participation prior to treatment

3.2 Subject Accrual and Study Duration

The pilot study will have an active enrollment period of approximately 5 months before the transition phase, up to 3 months for the transition to the intervention arm, and then 5 months after the study intervention is introduced. All participants are children.

4 Overall Study Design

4.1 Overall Research Question

The overall research question is, does implementation of the prehospital treatment bundle, including ipratropium and dexamethasone, affect outcomes for children with a 911 EMS activation for life threatening wheezing/asthma? Our long-term goal is to conduct a pragmatic trial using a hybrid stepped-wedge design to evaluate the implementation of an evidence-based EMS protocol for children with life-threatening wheezing/asthma. This is a critical research question, and if we find benefit, the study will have a substantial impact on outcomes for children with life-threatening wheezing/asthma. The trial is also valuable if negative. EMS agencies invest significant resources in preparing to treat children with acute life-threatening wheezing/asthma. This includes stocking medications and training providers. EMS agencies have limited resources and typically devote 4 hours in total per year training for all pediatric conditions. Our intervention is something that can be accomplished within these limitations. Clinical trials are needed to help EMS direct the limited resources available for pediatric care to treatments that are known to improve outcomes. We anticipate that study-specific training would be an hour or less for EMS providers and will be feasible to implement within typical EMS agency training programs.

4.2 Treating Wheezing Children Earlier Will Improve Outcomes

The overall premise of this project is that earlier treatment of wheezing children who have life-threatening asthma/wheeze will improve patient outcomes. Systemic corticosteroids given in the ED are effective in reducing hospital admission rates in children 2–17 years who present with acute wheezing, and nurse-administered steroids given early in the ED course are linked with reducing the hospital admission rate from 19 to 12%.^{13, 16, 18, 19} Also, administration of inhaled ipratropium in the ED has been shown to reduce hospital admission rates in children.^{19, 23}

Early systemic steroids and inhaled ipratropium treatments are now standard of care for pediatric EDs when treating non-bronchiolitic wheezing in children. These treatments are also recommended for EMS agencies by large national organizations.^{24, 25}

However, few EMS agencies have incorporated these treatment protocols, offering us an opportunity to implement a treatment bundle and study its impact on patient outcomes. Table 1 shows current medications included in EMS protocols across several PECARN-affiliated EMS agencies. Of note, few sites use inhaled ipratropium, and even fewer use dexamethasone, which is best for pediatrics because it can be given orally, IM, or IV. Many sites have protocols that incorporate IV magnesium, though it is rarely used in children and has an increased risk of adverse effects compared to ipratropium and dexamethasone.

4.3 EMS Can Deliver Treatment Earlier

Paramedics may be able to deliver essential treatments over an hour earlier than the Emergency Department. Data from the children's hospitals in the PECARN registry show significant gaps in the timeliness of ED treatment for wheezing children. Among patients who went on to be hospitalized for wheezing, 41–85% were treated with systemic corticosteroids, 51–76% with three or more albuterol treatments, and 64–88% received ipratropium within 1 hour of ED triage. An evaluation of over 36,000 PECARN patients indicated that the mean time to the initial dose of steroids was 81 minutes. Among our sites, EMS spends an average of 29 minutes with patients (on scene + transport), so there is sufficient time to implement the protocol. Thus, administration of these treatments in the EMS environment will improve treatment times by more than 1 hour in most patients and likely offers similar benefits to nurse-initiated steroids.¹³ Emergency physicians may decide whether to admit or discharge a patient based on how long the patient has been in the ED since length-of-stay is a valuable metric and quality measure for ED care.²⁶ Thus, when a respiratory treatment is started earlier, the patient likely has less respiratory distress when a disposition decision is made and is more likely to be discharged. (Figure 1)

4.4 Clinical Treatment Bundle for Wheezing Children

We will adapt the patient treatment protocol published in the “National Model EMS Guidelines” developed by the National Association of State EMS Officials (NASEMSO) after a systematic review.²⁵ The NASEMSO treatment protocol includes albuterol treatments repeated as needed, up to three ipratropium treatments, dexamethasone given by any route (PO/IM/IV), intramuscular epinephrine if no improvement, and IV magnesium for impending respiratory failure. We are studying these treatments as a bundle. The rationale is that prehospital care is protocol-driven, and bundling related treatments into a new care protocol is more pragmatic than changing one treatment in isolation. Additionally, the effect of bundled interventions is likely to be additive, and we expect that we will likely find a greater benefit to patients when the interventions are linked together. If the bundle is not effective, it is highly unlikely that individual elements will be beneficial.

If patients meet exclusion criteria, or decline study participation, they will be treated by their usual standard EMS protocol that was in place prior to starting the study.

Figure 2 displays the study protocol. Each agency will adapt this protocol to their own local format so it is consistent in visual appearance and presentation with their local standards. The dose of the nebulizer treatments is the same for all ages. Each agency is approaching dexamethasone dosing using a local approach. Charlotte and Buffalo already have protocols for dexamethasone dosing and will continue their current approach. The dexamethasone dosing in the protocol will apply to Utah, which does not currently use dexamethasone. It includes dosing instructions for dexamethasone based on length and weight with 2 doses for simplicity based on feedback from the EMS medical directors. The doses are as follows: 10–20 kg, 26–40” = 6mg/0.6 mL; > 20 kg, > 40” = 12 mg/1.2 mL. This dosing range for dexamethasone was selected based on the range of doses included in prior studies. Patients will receive between 0.3–0.6 mg/kg (or less, if > 40 kg) which is the typical range of doses that has been evaluated and found to be effective and safe in prior studies.

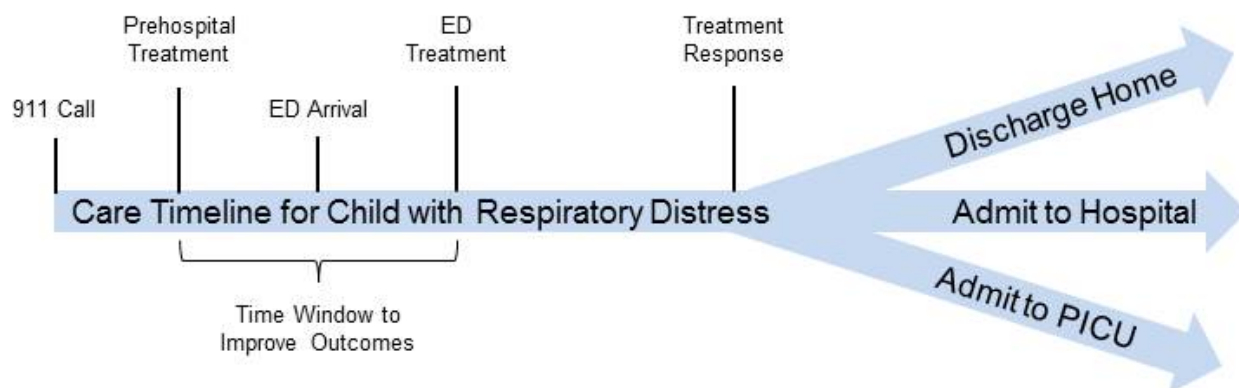


Figure 1: Study conceptual framework. By initiating treatment in the prehospital phase of care, patients may have more rapid improvement in symptoms and better outcomes.

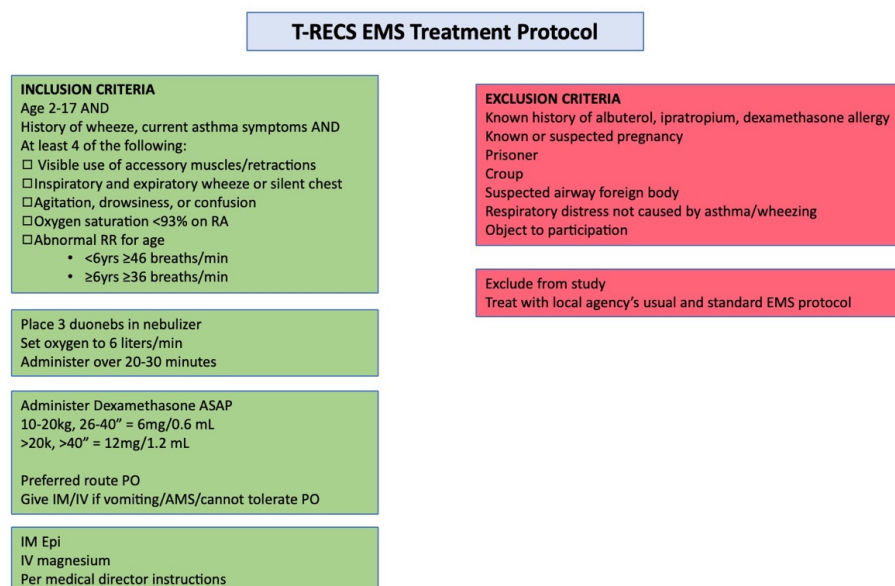


Figure 2: Study treatment protocol

4.5 Overview of the Future T-RECS Trial

In brief, the future T-RECS trial will be a prospective, randomized, hybrid stepped-wedge trial evaluating prehospital treatment of children with life-threatening wheezing/asthma among PECARN network EMS agencies. Both the pilot and full trials will be pragmatic trials designed to be conducted under real-world conditions. Thus, if the treatment bundle is effective in the study, we expect a similar impact when implemented in other EMS agencies.

A pragmatic pilot trial is the most appropriate design framework for the EMS environment since it is significantly less controlled than the hospital setting. Dr. Hansen was a co-investigator in the NHLBI-funded pragmatic airway resuscitation trial; an example of a successful pragmatic prehospital trial.²⁷ We anticipate 10–15 EMS agencies will participate in the future study with broad geographic, racial, and ethnic representation. Annual enrollment estimates are discussed below in the sample size section.

Table 2: Patients 2–17 years old treated with albuterol in 1 year

Study Site	Patients/Year
Salt Lake City (Salt Lake City Fire)	120
Charlotte (Mecklenburg County EMS)	238
Buffalo (Buffalo AMR)	120
	Subtotal: 478
Denver (Aurora Fire)	27
Seattle (Seattle Medic One)	49
Sacramento (Sacramento County EMS)	97
Alameda County EMS	124
Cincinnati (Cincinnati Fire Department)	96
Milwaukee (Milwaukee County EMS)	226
Houston (Houston Fire Department)	170
	Subtotal: 789

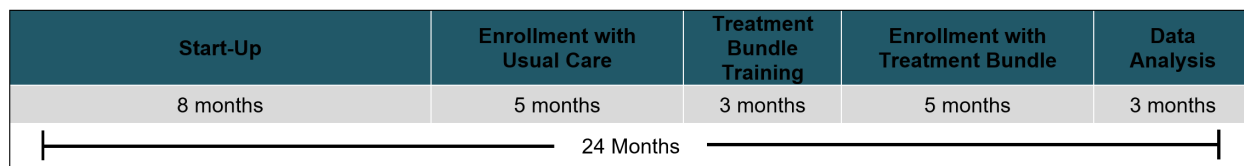


Figure 3: Example Timeline for Aim 2 Pilot Trial; treatment bundle training may be administered over shorter time period

Figure 3 depicts the overall study timeline at the three sites. This will be a prospective before-and-after study of a clinical treatment protocol and protocol checklist with approximately 5-month periods on either side of up to three months of EMS agency training on the treatment bundle (Table 3). The before-and-after design is similar to the hybrid stepped-wedge design that we will deploy in the full trial though we will not randomize enrollment start times due to the short duration of the pilot. The bundle requires training and medication formulary changes to implement and will not be feasible to randomize on an individual level. Staggered intervention has been implemented in the PECARN TBI-KT (computerized decision support study) and will be implemented in the prehospital PEDI-DOSE trial, and thus the future stepped-wedge trial is feasible in PECARN.

Table 3: Example site-specific pilot trial enrollment timeline

	Usual Care Enrollment (pre-bundle)				Transition enrollment (treatment bundle training)				Treatment bundle enrollment				
Site	Y1M09	Y1M10	Y1M11	Y1M12	Y2M01	Y2M02	Y2M03	Y2M04	Y2M05	Y2M06	Y2M07	Y2M08	Y2M09
1													
2													
3													

5 Study Procedures and Data Collection

5.1 Study Drug Administration

In the control or pre-transition phase, EMS agencies will follow their standard protocols for treatment. In the transition phase, EMS agencies are intended to continue their standard protocols, but the training during this period may influence their behaviors and as such this period is considered differently than the pre-transition phase. In the intervention phase, agencies will add any of the following medications missing from their treatment protocols for children who meet eligibility criteria: DuoNeb (albuterol and ipratroprium), dexamethasone. This collection of medications will be administered to children who meet eligibility criteria according to the treatment checklist from Aim 1.

5.1.1 Acquisition

Each agency will acquire the medications using their normal procedures for acquiring medications.

5.1.2 Preparation, Storage & Labeling

Individual agencies will determine how to store the medications in their vehicles. Refrigeration is not required. The medications all come in labeled packages.

6 Data Collection

6.1 Prehospital Data Collection

Table 5 lists example study variables. The primary method for identifying study participants will be prehospital data reports generated by EMS agencies. Each participating agency uses an electronic medical record with discrete fields for data elements of interest in the study. An online data collection tool (self-report) will also be used to collect data from paramedics regarding the care they administered to the enrolled patient in order to promote consistent data collection. We will

Table 4: Study variables – Primary variables to collect in the study

<u>EMS Patient Care Report:</u>	<u>ED Record: Obtained by RC abstraction</u>	<u>Inpatient Record (if patient admitted): Obtained by RC abstraction</u>	<u>Parent/Subject Report</u>
E.g., Name, age, sex, date of birth, date of service. Estimated height and weight. Vital Signs (respiratory rate, heart rate, blood pressure, oxygen saturation) Medications administered (for study drugs: doses and times; for epinephrine, IV magnesium, and non-study corticosteroids: dates and times). Other interventions and times (oxygen, assisted ventilation, endotracheal intubation, etc.) On-scene arrival time, patient encounter time, transport start time, hospital arrival time, distance traveled, destination hospital. Primary impression(s). Eligibility criteria. Adverse events.	E.g., Name, age, sex. Initial vital signs. Initial asthma severity score (CAS, PAS, PASS, PRS, etc.), subsequent asthma severity score. Demographic variables and insurance status. ED primary diagnoses. Medications administered, doses, and times. Other interventions (oxygen, assisted ventilation, intubation, etc.) ED disposition (home, admit, PICU admit). ED Length of stay. Eligibility criteria. Adverse events.	E.g., Hospital length of stay. Discharge diagnoses. Major respiratory interventions (CPAP/BiPAP, endotracheal intubation, tube thoracostomy, mechanical ventilation, high flow nasal cannula, continuous albuterol). Adverse events. Ventilator and ICU free days at day 28	NIH PROMIS asthma Impact Score. Demographic variables and insurance status Outcome variables such as admission and discharge status and dates

obtain the medical records for patients who meet the eligibility criteria. Research coordinators at each site will input data from EMS and hospital records into a database managed by the DCC. The medications and treatments section of the prehospital records are generally considered to be highly accurate.

We will have paramedics complete the online self-report, accessible via a QR code or link for any child age 2-17 years treated with albuterol and transported for a 911 response. The self-report will include study inclusion and exclusion criteria to allow for identification of eligible patients. As a backup, we will review the medical records to identify inclusion criteria, and contact paramedics if the documentation (prehospital medical record or EMS self-report form) is not clear. This is a similar procedure currently being used in the prehospital PediDOSE study.

6.2 Hospital Data Collection

Research coordinators at each site will attempt to obtain hospital data for each participant (Figure 4). They will follow established protocols for accessing using electronic health records at each primary children's hospital. It is anticipated that the ability to collect EHR data will depend on which hospital the participant is transported to. Each site will determine which hospitals are appropriate for EHR hospital data collection based on local EMS transport patterns and the feasibility of data collection.

The community hospital data collection processes have been used at several PECARN and T-RECS sites, including Portland, through participation in other adult prehospital research networks such as the Resuscitation Outcomes Consortium. We estimate that 40% of patients will be transported to local community hospitals vs. 60% to PECARN hospitals. Evaluating the feasibility of collecting outcome data for children transported by EMS to a wide range of hospitals is one of the primary aims of this study. Though the Portland site is not enrolling, it is overseeing the study, and has a long history of prehospital research and collaborations with the local non-academic health systems and will provide a model for other sites. Previously successful methods include establishing a direct portal into the electronic health record to abstract hospital data, traveling to local hospitals to use an on-site portal to the medical record, or using a community hospital data abstractor if available.

6.3 Emergency Department Screening

Patients arriving at study affiliated EDs will be identified in real-time during research coordinator hours as the RCs monitor incoming ambulance arrivals for potential study patients. Sites will also establish notification procedures that will allow daily screening of eligible patients who arrive at outside hospitals where protocols for study data collection have been established and at those who arrive during RC off-hours. This will be done in order provide notification to parents and subjects at the earliest feasible opportunity.

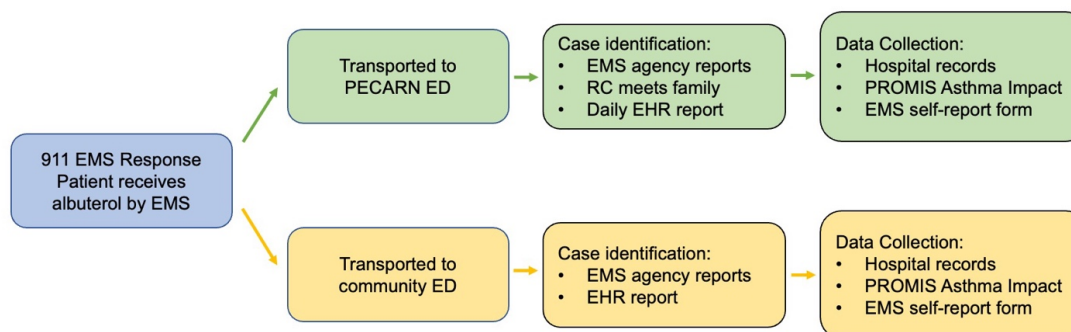


Figure 4: Data collection from PECARN-affiliated Children's EDs and community hospital EDs

6.4 Follow-up Data Collection

Subjects/parents who did not refuse contact for follow-up, will be asked to complete the NIH PROMIS asthma impact score on day 6, with reminders on days 8 and 10. The score will be completed by a parent proxy for children aged 5—7 and, when feasible, by the patients aged 8—17 themselves. The families will be provided with a \$50 incentive to complete follow-up. Certain study outcomes such as hospital admission and discharge dates may also be collected by parent/guardian report at this time.

We will also review the chart for 28-day ICU and ventilator outcomes to determine the ventilator and ICU free days for each subject.

6.5 Study Data Collection Monitoring

Given the short duration of the study, we will evaluate the number of enrollments and general adherence to the study protocol on a biweekly basis, especially during the intervention phase. This will allow us to investigate potential causes, reinforce the protocol, provide additional just-in-time education, and improve adherence during the short 5-month intervention window.

7 Data Analysis

7.1 Study Outcomes

Key quantitative analyses of Specific Aim 2, to demonstrate feasibility of conducting the larger trial, focus on two outcomes. The primary outcome is the ability to determine whether a hospitalization resulted. The secondary outcome is the collection of the PROMIS asthma impact score. Mortality is a safety outcome; although the study has not been powered to detect a difference in mortality, it is important to assess the risk of mortality with different treatment strategies when life-threatening conditions are present.

Other outcomes pertaining to Specific Aims 1 and 3 are described elsewhere in this section.

7.2 Specific Aim 1: To develop and produce the protocol checklist

The goal of this aim is to prepare a simple treatment checklist that will enhance training and delivery of care. The eligibility criteria are limited to specific signs and symptoms representing life-threatening wheezing/asthma. The checklist will guide EMS personnel through the eligibility criteria as well as the treatments. Checklists have been shown to improve guideline compliance in hospital-based care and have also been shown to improve quality of care and protocol adherence in the EMS environment for adult patients, though use in pediatric EMS patients is novel.^{1–3, 28, 29}

A checklist typically results in a 10–20% overall improvement in protocol adherence.^{2, 29} In this study, we will implement the checklist to include the study eligibility criteria and improve protocol adherence while keeping the study pragmatic so that our results can be generalized to other EMS agencies not supported by pediatric EMS researchers and trials. In this aim, we will adapt a checklist initially developed by Snohomish County Washington Fire Department (Figure 3). We have modified this checklist to be consistent with the NASEMSO EMS pediatric wheezing guidelines.²⁴ Using the checklist, Snohomish Fire was able to improve albuterol/ipratropium use to over 70%. We are starting the treatment bundle with an albuterol/ipratropium combined nebulizer rather than an albuterol nebulizer treatment alone. This simplifies the process for the paramedic since these two medications come as a “DuoNeb” in a single ampule and will make it much easier to adhere to the protocol.

7.2.1 Checklist Format

The content of the checklist is adapted from the NASEMSO guidelines (Figure 3) and has been accepted by medical directors in the pilot. In this part of the study, we will focus on the checklist format, ensuring that it is acceptable for use by field providers, their managers, and medical directors, and packaging it for deployment. We will use existing PECARN EMS advisory committees where available and otherwise consult with EMS providers to The EMS operations committee will determine the best methods of implementation (paper, electronic, pocket card) and provide feedback

on format. The study team will then revise and distribute the checklist to the agencies for final internal review and approval. We have obtained preliminary data on checklist implementation from several EMS agencies within the CHaMP Node of PECARN. Most agencies will deploy the checklist as an electronic document. One requested a pocket card. No agencies in CHaMP can deploy the checklist in the EHR. We also received feedback on the checklist from EMS medical directors who will participate in the pilot. We revised the checklist until we reached a consensus that it was acceptable for use among several key agencies.

7.2.2 Checklist Education

We will engage various stakeholders including participating EMS agency medical directors and practicing paramedics to identify best practices for checklist education and roll-out. These will take the format of conference calls and a survey of agency leaders if needed. Our goal is to support each agency while allowing the use of routine processes to implement new protocols. We will obtain feedback from the agencies and refine the tip sheet.

7.2.3 Potential Problems and Alternative Strategies

We believe the risks to this aim are low. All participating EMS agencies have indicated it is feasible to use the checklist within their organization. We may find that agencies have different needs in the format or deployment of the checklist and will accommodate those needs through this study.

7.3 Specific Aim 2: Evaluate the feasibility of collecting the study outcomes

Primary Hypothesis: We will collect hospital admission status for 80% of patients.

In this aim, we will establish the feasibility of collecting the study outcomes. We estimate 60% of patients will be transported to EDs of PECARN-affiliated hospitals where data collection has been demonstrated. We need to establish the feasibility of collecting the hospital admission status at non-PECARN hospitals. We will also test the feasibility of collecting the NIH PROMIS asthma impact scale. However, the feasibility of collection is uncertain in a prehospital trial where patients disperse to several hospitals, many without research infrastructure.

Because Specific Aim 2 pertains to the feasibility of collecting study outcomes, we will summarize the proportion of enrolled patients for whom the primary outcome is collected, overall, and by site. We will similarly summarize the secondary outcome. We will construct one-sided 95% exact binomial confidence intervals for each such proportion, overall and by site, to provide the interval's lower bound for each capture proportion. The lower bounds will be useful to gauge the relative feasibility of using hospitalization or the PROMIS asthma impact score as a primary outcome in the future trial. We anticipate that the hospitalization outcome will be collected for at least 80% of enrolled patients overall, and at least 70% at each site. We anticipate that the PROMIS

asthma impact score will be collected for at least 60% of enrolled patients overall, with substantial variability across sites.

To better understand potential biases in study design, implementation, and statistical conclusions, additional analyses will include evaluation of patient characteristics of patients transported to the primary children's hospital EDs vs. community general EDs and description of patients not treated with prehospital albuterol who were treated with albuterol within 30 minutes of ED arrival. We will compare variability in the capture of the outcomes between subgroups defined by 1) age group, i.e., 2–4, 5–10, and 11 +, and 2) specific eligibility criteria met by participants, and 3) black vs. non-black race, and 4) sex. For these additional analyses, missing data will be addressed using multiple imputation.

We will also measure the percent of eligible patients treated with ipratropium and dexamethasone at each site, which we estimate will be 55–65% in the post-transition phase, based on work at Snohomish Fire and previous studies. These differences will be summarized overall and between subgroups defined by time with the patient (< 20 minutes vs. 20 + minutes) and other factors from the previous paragraph. The 20-minute subgroup is an initial hypothesis that will be reviewed with the medical directors and potentially revised based on the collected data.

We will evaluate efficacy by comparing the hospital admission rate between pre-transition and post-transition groups; those enrolled during the transition phase will be summarized for informal comparison but not considered in the primary efficacy analyses. We will also evaluate ED length-of-stay, and the first asthma severity score obtained in the ED. As safety outcomes, mortality, ICU admission, and endotracheal intubation rates will be reported pre- and post-implementation of the treatment bundle, including the transition phase. The reported rates will be accompanied by 95% confidence intervals of their differences between the post-transition and pre-transition phases. Because mortality is expected to be uncommon, additional analyses of mortality rates may be conducted but would be considered exploratory in nature.

7.4 Specific Aim 3: To evaluate the implementation using the RE-AIM framework

7.4.1 Rationale

In this aim, we will evaluate the implementation of the study protocol from the perspective of the patients, providers, and the EMS system using the RE-AIM framework.⁴ In Aim 1, we prepared a checklist that is a vital component of the implementation plan. Each agency will use the educational processes that they typically use for new protocols, enhanced by training materials provided for the study. It is critical to evaluate the real-world implementation of this treatment protocol in the pilot so that we can make the process as efficient and effective as possible in the full trial. The RE-AIM framework is ideal for this study as it allows us to understand implementation from perspectives that are highly relevant to the prehospital system.

Table 5: RE-AIM questions for evaluating the implementation of the treatment protocol

RE-AIM Dimension	Key Questions to Answer
Reach	<ul style="list-style-type: none"> • Rate of treatment administration by age, sex, and race out of all potentially eligible • Rate of treatment administration by disease severity (initial respiratory rate)
Effectiveness	<ul style="list-style-type: none"> • Number of patients ages 2-17 and received study-specific medications but were not eligible upon further review
Adoption	<ul style="list-style-type: none"> • Number of individual paramedics who used ipratropium and dexamethasone during the study <ul style="list-style-type: none"> ◦ Was use clustered among a smaller than expected group of providers? ◦ Did the age, years of experience, and sex of providers who did and did not use protocol differ? • Did specific organizations adopt more completely than others? <ul style="list-style-type: none"> ◦ Fire vs. transport agencies ◦ Across study sites
Implementation	<ul style="list-style-type: none"> • How well was the treatment protocol adhered to? • How did transport time/distance influence adherence to the treatment protocol?
Maintenance	<ul style="list-style-type: none"> • What do providers think will be required to maintain protocol (cannot fully evaluate maintenance due to 5-month enrollment period of the pilot study)

7.5 Approach (Table 5)

Reach: We will use demographic data to describe the characteristics of patients treated with the study protocol in comparison to those treated with standard treatment. We will monitor for differences in age, sex, race, and illness severity. We will specifically evaluate for disparities in implementation among racial and ethnic minorities as well as among males and females.

Effectiveness: This pilot study is not designed to show a difference in clinical outcomes. We will evaluate the application of the treatment protocol to identify patients who had the protocol misapplied. We will do this by evaluating the number of patients who received study treatment but were found to be ineligible. We will also identify ED and hospital diagnosis ICD10 codes of enrolled patients, when available, to determine if these diagnoses included any indication for bronchodilator treatment or an alternate diagnosis such as croup. We will also evaluate the time saved by prehospital steroid administration in the post-implementation phase. Although the T-RECS trial was not powered to reach conclusive determinations about the efficacy of the post-intervention phase, pre-specified analyses of interest include some analyses that pertain to efficacy. These include comparison of hospitalization rate, PROMIS Asthma Impact Scale, 28-day ventilator-free days, 28-day ICU-free days, ED length of stay, and first asthma score in the ED between the pre-transition and the post-transition phases.

Adoption: We will describe the providers who applied the protocol during the study compared to the agency's general workforce. This will help us determine if our training missed or was less effective with certain groups, such as more or less experienced providers.

Implementation: We will use data from the pilot project to establish the expectations for compliance with the treatment protocol based on time spent with the patient and the transport time to the hospital. **We do not consider protocol adherence to be all-or-nothing but will determine which steps should be completed based on the time the providers spend with the patient.** However, we consider the minimum necessary to be compliant is administering at least one DuoNeb treatment and dexamethasone. Since the treatment bundle has multiple sequential steps, the ability to complete these steps depends on the time available to the treating paramedic. For very short transports, we would expect providers to complete fewer steps. We will analyze what is feasible to complete based on the transport time and establish time-based norms for protocol completion that will assist in developing our analysis plan for a future trial. However, we will likely consider the minimum needed for protocol completion to be one albuterol/ipratropium (DuoNeb) treatment and one dexamethasone treatment. Evaluating the timing of interventions will also allow us to stratify analysis by total time with patient and transport distance time, provided there are adequate numbers of patients in each stratum.

Maintenance: This pilot trial has short enrollment periods and will not be able to evaluate long-term maintenance. However, we will track protocol adherence over time as a method to assist in

understanding any study-specific agency training or quality assurance activities that took place after the study started. We will also conduct a paramedic feedback survey. Paramedics participating in the feedback survey will be an active employee of an affiliated/participating EMS agency with current certification. Paramedics will be identified by medical directors, training officers, or other agency personnel. Recruitment will occur via email and/or posting a survey link or QR code during events or in public work areas. Paramedics may receive a series of up to three communications over two weeks for recruitment purposes.

7.6 Sample Size Justification

The proposed study is focused on assessing the feasibility of a larger study and is not equipped to determine the efficacy of the intervention. Table 2 reveals that approximately 39 patients per month are treated with albuterol across the three sites; although Salt Lake City Fire's participation in this study has been replaced with Unified Fire, we expect similar if not greater numbers from Unified Fire. We initially estimated about 15 patients ages 2–17 per month over the ten months of enrollment would be enrolled, so the projected enrollment for the study would be 150 for the pre- and post-transition phases.

With this sample size, if the true capture rate of PROMIS asthma impact scores were 60%, the expected lower bound of the interval would be 53%. Under the same assumptions, if the true capture rate of hospitalization status were 80% at each site and all observations were independent, the expected lower bound of the one-sided 95% confidence interval for the overall capture rate would be 73.9%. Thus, the capture rates may be estimated with sufficient precision to assess the feasibility of each outcome for the larger trial if there are 150 enrollments during the pre- and post-transition phases, combined, which would be an enrollment pace of 5 enrollments per agency-month (three agencies with five months pre-transition and five months post-transition). However, the initial enrollment pace of two enrollments through approximately four agency-months of enrollment suggests that the total enrollment during these phases is likely to be much closer to 15 than to 150. Under the same assumptions as above with the exception of a sample size of 15, if the true capture rate of hospitalization status were 80% at each site and all observations were independent, the expected lower bound of the one-sided 95% confidence interval for the overall capture rate would be 56.7%, and if the true capture rate of PROMIS asthma impact scores were 60%, the expected lower bound of the interval would be 36.6%. Although the precision of estimation is low if enrollment is low, if the percentage of PROMIS Asthma Impact Scores collected is either very low or very high, we believe this would give our team valuable information for planning the future trial. Optimistically, the combined enrollment during pre-transition and post-transition phases might be closer to 22 given variation in patient encounter volumes; however, the updated enrollment projection is much less than 150 unless there is a fundamental change to the trial. A reduction in enrollment would limit the precision of our statistical analyses for aims 2 and 3. However, there are many benefits to the current study and the information we gain will aid in refining logistical processes to plan for conducting a larger scale trial.

The earlier estimates were based off of screening criteria that are feasible to measure using retrospective review of prehospital medical records. We then considered that the hospital admission

rate for EMS arrivals is up to 50%, and thus expected those ill enough to meet eligibility criteria will be somewhat less than 50% of all patients who receive albuterol by EMS. The pilot trial will help us develop a better understanding of our expected enrollment for the larger trial. We will also gather important information on the performance of the eligibility criteria.

7.7 Human Subjects Considerations

This study involves implementing a treatment protocol for children with a 911 call for acute life-threatening wheezing/asthma. The treatment bundle is effective in the ED environment and is recommended by EMS specialty organizations. The patients in the pre-bundle phase will receive usual care. After the treatment bundle is introduced, patients are likely to directly benefit from study participation. Based on the very narrow therapeutic window for treating life-threatening wheezing/asthma, we plan to conduct the study under exception from informed consent regulations (EFIC) based on initial conversations with the single IRB. We will follow EFIC regulations for opting out, attempting prospective consent, and consent for data collection. These regulatory processes have been developed and implemented in multiple prehospital trials in the Resuscitation Outcomes Consortium. Our secondary outcome is the collection of the NIH PROMIS asthma impact scale, which involves contacting patients and parents by phone or electronically. We will prefer requesting in-person consent for this follow-up data collection where feasible as above and will seek to obtain consent by phone, mail, or email for other patients. Using our experience in this study, we will develop an EFIC toolkit for sites in the future trial. By the time our study starts, EFIC will have been implemented in PECARN PEDI-DOSE (NINDS U01 NS114042-01A1) and we will model their EFIC process.

7.8 Potential Problems and Alternative Strategies

All of the children's hospital EDs in this study have data collection infrastructure that has been used in previous research, so we believe the risk of data collection losses at the children's hospital sites to be low. There is more risk that selected community hospitals will have difficulty obtaining data, which is one of the main reasons to complete this feasibility study. Previous studies have shown that the most severely ill children are typically transported preferentially to children's hospitals, especially for respiratory distress.^{30, 31} Thus, we are likely to capture the patients who are most likely to benefit from prehospital stabilization. Furthermore, we will analyze prehospital characteristics of patients for all transport destinations, and we will compare the characteristics of patients who did and did not have outcomes available for collection.

We have evaluated the seasonality of albuterol administration within PECARN. During June, July, and August, rates of albuterol administration are about half of the other months of the year. Seasonal variability will not be a concern in the full trial due to longer enrollment periods. In the pilot, our overall outcome is feasibility, and our enrollment periods are longer than three months. Further, we investigated the hospital admission rate by season in PECARN and found that there is not significant seasonality in the admission rate with an admission rate range of 35%–45%. Further, the highest

admission rates (40–45%) were typically noted in the summer months when there are fewer overall visits.

In order to prepare for the full trial, we will evaluate ICD10 diagnosis codes, initial respiratory rate, and initial oxygen saturation to monitor for changes in patients being treated. The diagnosis codes will also help us understand the number of patients who are treated inappropriately, such as a child with croup being treated with nebulized albuterol instead of epinephrine.

8 Data Management

8.1 Clinical Site Data Management

Each clinical site will maintain study records in secure locations that may include password protected electronic files or locked filing cabinets. The site will maintain an Essential Documents Binder, which may be in paper or electronic form.

8.2 Data Coordinating Center

8.2.1 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 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 provides a secure, reliable, enterprise-wide infrastructure for delivering mission critical DCC systems and services to PECARN.

8.2.2 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 (UPS) 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, 7 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 (SAN) 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 (TB) 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.

8.2.3 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 Insurance Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems before access is provided.

8.3 Electronic Data Capture System

The Data Coordinating Center (DCC) will develop an electronic data capture system for this study. Currently the DCC uses multiple applications, such as OpenClinica or REDCap, and will elect to use the most appropriate application at the time of implementation of the study. Data will be entered by each clinical site.

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.

8.4 Study 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.

8.4.1 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.

8.4.2 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. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close out visit. The site initiation may take place as group training made up of site investigators and research assistants.

8.4.3 Remote Monitoring

The DCC may substitute 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.

8.5 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 Institutional Review Board (IRB) Approval

A single IRB (SIRB) will be used for this study. The University of Utah IRB will serve as the IRB of record. Study sites will rely on the University of Utah IRB to act as the IRB. The Data Coordinating Center and each clinical center must obtain IRB approval prior to participating in the enrollment phase of the study.

The Data Coordinating Center will track IRB approval status at all participating centers and will not permit participant enrollment without documentation of initial SIRB approval and local review

sign-off. The Data Coordinating Center will also track the maintenance of that approval throughout subsequent years of the project.

9.2 Informed Consent

9.2.1 Exception from Informed Consent

The T-RECS study involves emergency prehospital care of pediatric patients aged 2—17 years with life-threatening wheezing/asthma. All patients will have had a prior episode of wheezing. Asthma is the most common chronic illness in children with many affected patients, though only a small minority of children with asthma will call 9-1-1 in a given year.

There is no opportunity to consent these patients prior to their contact with the 9-1-1 system, since it would be impossible to predict who will contact the 9-1-1 system for life-threatening wheezing/asthma in the future. These patients need immediate treatment and there is not sufficient time to obtain informed consent from a legally authorized representative (LAR) prior to starting the treatment. The therapeutic window for initiating our intervention, the treatment bundle, is zero minutes, since the treatment bundle will be initiated as soon as paramedics note eligibility criteria for life-threatening wheeze/asthma are met (see criteria above) and no exclusion criteria are met. Respiratory distress from acute wheezing is life-threatening and can be fatal if left untreated. The disease severity worsens with time, so treatment must be initiated as quickly as possible. These treatments will typically be administered by paramedics after a 9-1-1 call for life threatening respiratory distress. In addition to the therapeutic window of zero minutes, a LAR may be unavailable for children who are experiencing symptoms and needing treatment away from home, such as at school, daycare, sports, or other similar activity. It is vital to include acutely ill children in emergency care research. Even if there were time to obtain fully informed consent prior to starting treatment for life-threatening wheezing/asthma, it is likely that this could be perceived as coercive by parents who want treatment started as soon as possible after a 9-1-1 call. Based on these factors, we will enroll patients using exception from informed consent (EFIC).

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

Acute asthma is *life-threatening and available treatments are unsatisfactory or unproven*.

21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

This study will enroll children with life-threatening asthma/wheeze based on the strict eligibility criteria. Asthma attacks requiring a 911 call have a higher risk of being life-threatening. One

study found that as many as 82% of children with a 911 call for wheezing who have respiratory distress defined as an abnormal respiratory rate will require ICU or immediate care admissions.¹² This highlights the high-risk and life-threatening nature of EMS responses for wheezing children compared to other populations.

Our study will improve the effectiveness of treatment for life-threatening wheezing/asthma in the prehospital environment. Severe asthma remains a life-threatening condition in pediatric patients, that also has substantial morbidity. The large majority of pediatric asthma deaths occur outside the hospital where EMS providers respond.^{32–35} The morbidity is significant and can include requiring endotracheal intubation, ICU stays, pneumonia, and barotrauma including pneumothorax. There are several treatments that have demonstrated efficacy in the hospital/ED environment including dexamethasone and ipratropium, yet these treatments are unproven in the EMS setting. These treatments have been standard of care in pediatric Emergency Departments for more than a decade, but have not been widely implemented or studied in EMS. Children who receive prehospital treatment after a 911 call for acute wheezing tend to be more severely ill compared to those who arrive to the ED by other means, and there is very limited evidence from the EMS setting, so there is significant need for proven treatments for pediatric patients with life-threatening wheezing/asthma in the EMS setting.

All EMS agencies use albuterol to some extent for acute wheezing. Some agencies have corticosteroids available, but most limit to medications that can only be given through an IV, limiting applicability in pediatric patients. Relatively few agencies use ipratropium for acute wheezing. A retrospective study suggested that implementing prehospital dexamethasone, which can be given orally, IM, or IV, was effective at reducing hospital admission rates when compared to a protocol that only included an IV steroid.³⁶ There is no prospective data on the use of the key elements of the treatment bundle, including ipratropium and dexamethasone, from pediatric patients in the EMS environment. Though these treatments have been extensively studied in hospital Emergency Departments, they remain unproven in the EMS environment, which is significantly different from the hospital, such that the results from hospital-based studies may not be generalizable to the EMS environment. Some EMS agencies have implemented the bundle based on hospital data alone without safety or efficacy data from EMS.

Obtaining prospective informed consent is often not feasible.

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

The study intervention includes a new EMS treatment protocol for children with life-threatening asthma/wheezing with an accompanying checklist. This checklist includes oxygen, repeated bronchodilators, and systemic corticosteroids. These interventions must be administered immediately and there is not time to gain consent from a LAR before starting the treatments, because the therapeutic window is zero minutes.

Our study hypothesis, and previous ED-based data, have shown that the earlier the treatment is started, the better the patient outcome will be. It is not feasible to identify which patients will need EMS care for acute life-threatening wheezing/asthma in advance. The patients enrolled will include some children with chronic asthma, but will also include children with wheezing induced by respiratory viruses. Further, there are so many chronic asthmatics in the US, it is not feasible to prospectively consent them.

The study subjects in this case are children, who are not able to provide their own consent due to age. Further, some children will be away from their parents (most common LAR) when the need for prehospital care arises. Many children will be at school, daycare, sports, or with a babysitter when the problem arises and there will not be someone immediately available to provide consent. Unfortunately, the specific locations of EMS calls for pediatric wheezing, and distribution of cases with and without a LAR present, are not known. Also, our intervention is an entire treatment bundle and EMS treatment protocol. It includes treatments such as oxygen and albuterol that are commonly used in EMS as well as ipratropium and dexamethasone which are standard-of-care in the ED but infrequently used in EMS. It is not possible to split the bundle into individual components in the study design and start some treatments while obtaining consent for others, as the medications are given simultaneously in the protocol. Albuterol and ipratropium are administered simultaneously as a nebulizer treatment using a commercial combination product (Duoneb), and oxygen from a tank is used to nebulize the medications, therefore all three treatments are started simultaneously in the bundle. Dexamethasone is given immediately after.

Participation holds prospect of direct benefit to subjects

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

Participation in T-RECS offers the prospect of direct benefit to study participants. We will be applying more aggressive treatment to children with a life-threatening condition that has proven efficacy. Studies performed in the ED have demonstrated that earlier administration of dexamethasone and ipratropium are associated with more rapid resolution of symptoms and lower odds of hospital admission and ICU admission. Further, our protocol increases the amount of albuterol that can be administered before hospital arrival, which has the potential to lower the risk of death or severe morbidity to a greater extent than the current standard which often limits to 2 treatments depending on the agency.

The best evidence for ipratropium comes from the randomized trial published by Qureshi et al. in NEJM in 1998 where among those with severe asthma the hospitalization rate was reduced from

52.6% to 37.5%, and Iramian et al had similar results.^{19, 37} A 2013 Cochrane review similarly concluded that combined albuterol/ipratropium is more effective than albuterol alone.³⁸ Steroids are considered the primary treatment for children with non-bronchiolitis related wheezing in the pediatric ED. There is good evidence to suggest that earlier administration of steroids in acute wheezing, including life-threatening wheezing, improves outcomes. This includes a study by Zemek et al. where nurses were administering dexamethasone in triage prior to seeing a physician resulting in 0.56 times the odds of hospital admission if steroids were given in triage.¹³ A prehospital study by Nassif et al. found that introducing oral steroids through a protocol change to children 2–18 years of age treated by EMS for an asthma attack significantly reduced the hospitalization rate from 30% to 21%.¹² A 2001 Cochrane review supports the notion that steroids reduce the hospital admission rate and a 2012 study by Bhogal et al. demonstrated an association between timely delivery and lower hospital admission rates.^{14, 18} These studies provide the justification for benefit to study subjects. Our study will allow EMS providers to deliver these highly effective treatments significantly earlier than they would be given under the current paradigm (50 minutes earlier on average).

The risks of the treatments are reviewed below in [Section 9.5](#) in detail. Our study primarily relates to children receiving the treatments which would be provided in the ED earlier by giving them in the EMS setting. We will train the paramedics on the eligibility criteria to reduce the risk of violations. We will also track potential violations of the eligibility criteria to evaluate the potential for children to receive study treatment who would not otherwise be exposed to them in the hospital.

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

The study will enroll only children with life-threatening asthma. We are studying a treatment bundle with three medications and plan to administer them simultaneously to maximize the potential improvement in outcomes.

This research could not be carried out without EFIC because the treatment bundle for life-threatening asthma/wheeze after a 9-1-1 call needs to be given immediately after paramedics arrive on scene. Paramedics cannot wait to obtain informed consent prior to starting the bundle for a child with acute life-threatening asthma/wheeze. The therapeutic window is zero. We also believe it will be unacceptable to LARs to wait for study consent prior to starting treatment and they may feel coerced into participating so their children could get the best available treatment. National EMS organizations recommend the treatment bundle we are studying as accepted best practice and some US EMS agencies have implemented it.²⁴

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

We define the therapeutic window as zero minutes based on the revised eligibility criteria. Enrolled children will be experiencing life-threatening respiratory distress. The study intervention is an entire treatment bundle and EMS treatment protocol change throughout an EMS system covering a specific geographic area. We cannot anticipate which patients will be treated by EMS and prospectively obtain consent.

The scientific evidence for the therapeutic window for dexamethasone is found in a 2012 study by Bhogal et al. In this study, investigators demonstrated that timely steroid administration was linked to lower hospitalization rates and shorter required times for active treatment in the ED.⁷ There was no lower bound or threshold in this study, providing justification for the therapeutic window of the bundle being 0 minutes.

The patients enrolled in the study will be experiencing life-threatening asthma/wheeze based on our eligibility criteria. Previous studies have found that children with a 9-1-1 EMS activation for acute wheezing and respiratory distress have more severe symptoms and are more critically ill than children who arrive in the Emergency Department by other means such as private vehicles.³¹ Children who arrive by EMS to an ED have five times the odds of being critically ill and nearly three times the odds of requiring hospitalization than those who arrive by other means.⁸ The therapeutic window for treatment of a child with life-threatening wheeze/asthma with our treatment bundle is zero.

We commit to trying to obtain prospective informed consent from the LAR in the therapeutic window, if feasible. We will provide a summary of our efforts to obtain informed consent to the IRB at continuing review.

Our proposed treatment bundle uses combined albuterol/ipratropium nebulizers and dexamethasone. The use of the combination nebulizer product is a critical part of the protocol to simplify care in the field during a stressful scenario. Paramedics rarely care for children with respiratory distress, so our goal is to simplify and reduce cognitive load while providing the highest level of safe care possible. Since albuterol has been the standard of care for initial treatment of acute wheezing with respiratory distress for decades, there is not any available evidence that suggests withholding this treatment for any period of time is acceptable. Further, albuterol is a home treatment that is often used for wheezing children prior to EMS arrival. Albuterol is the mainstay of EMS protocols for acute wheezing, and we believe withholding this medication for any period of time is unethical thus making the therapeutic window zero minutes. It is not feasible to withhold ipratropium in our study protocol, since the medications are being used as a combination product for the reasons outlined above. A Cochrane review from August 2013 found that the combined administration of albuterol and ipratropium was effective in reducing the rate of hospital admission compared to albuterol alone.

9.3 Community Consultation

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 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. Each site will have its own individualized consultation plan to meet the needs of its specific community.

9.4 Disclosure, Opt Out, Informed Consent, and Withdrawal

Pre-study public disclosure:

Before the clinical investigation starts, we will notify the public in the participating communities that the study will be starting. We will include information on the risks and expected benefits. We will use social media including Facebook and X (formerly known as Twitter), and will also use press releases from the healthcare systems involved to notify the public.

Opt-out:

We will not use opt out bracelets or other physical means of signaling objection to study participation. If a subject, LAR or family member expresses to the treating paramedic a desire to not participate in the study, the patient will be treated with the EMS standard protocol similar to those excluded for other reasons.

Informed Consent Procedures:

We commit to obtaining prospective informed consent from the parent/LAR when feasible within the therapeutic window to obtain prospective informed consent. We commit to attempting to contact a family member if a parent/LAR is not available to provide the opportunity to object to study participation within the therapeutic window. These efforts to contact the parent, LAR and/or family member will be summarized and made available to the IRB at the time of continuing review.

We will use a brief online video to provide an overview of the study that will cover all required elements of informed consent, when feasible. This will be available by QR code for paramedics to provide to LARs or family members. We will use this brief video to provide study information when feasible. This will be approved by the sIRB before implementation as a part of the e-consent process. Following the instructional video, LARs can verbally indicate whether or not they agree to participate. When feasible, informed consent will be conducted following the video presentation. A phone number will be provided by paramedics to the parent, LAR, or family member, if present, for them to ask questions about the study. All study team members who will be on-call will be trained in the study protocol, the risks/benefits, the EFIC process, and will be able to obtain informed consent and answer any study questions.

We will contact the parent at the earliest feasible opportunity, or if the parent is not reasonably available, a LAR, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. When feasible, we will contact them in-person in the Emergency Department (ED) prior to admission to the hospital or discharge from the ED. In-person

contact in the ED will only be feasible in primary PECARN EDs when a research coordinator is on site. For children who are admitted to the hospital from the ED, if in-person contact is not feasible in the ED, we will attempt in-person notification and consent for ongoing data collection when the patient is in the hospital at the earliest feasible opportunity whenever possible. If in-person notification is not feasible, or the opportunity is missed, we will use telephone notification and consent for ongoing data collection at the earliest feasible opportunity, and if that is not feasible, we will contact the LAR by mail or email. We will make every effort to identify eligible participants in real-time, within 24 hours of ED admission, though there are sometimes screening delays in obtaining medical records, contacting paramedics to confirm eligibility, and/or obtaining necessary translation services. We commit to contacting families at the earliest feasible opportunity after enrollment is confirmed. If obtaining informed consent is feasible, consent shall be documented in accordance with 21 CFR 50.27(a) by the use of a consent form approved by the IRB and signed and dated by the subject or the subject's LAR at the time of consent and a copy shall be given to the person signing the form. If a subject or LAR decline participation or a family member objects, the patient will receive standard EMS care. When we contact the subject, LAR or family member we will inform them that the subject was in a study, we will review the study goals, medications, and outcomes, and we will inform them that participation can be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a LAR or family member is told about the clinical investigation and the subject's condition improves, the subject will be informed as soon as feasible.

We anticipate all subjects enrolled in this study will be children. For all subjects who are children, we will not only notify the parent, LAR, or family member, but will also provide age-appropriate information to child subjects. Subjects who have the ability to provide assent will be approached to obtain assent for ongoing study participation according to site-specific requirements outlined by the local site Human Research Protection Program (HRPP).

The parental permission and assent forms will be used to obtain (1) prospective consent (when feasible) prior to enrollment and (2) notification of enrollment and to obtain consent and assent for ongoing data collection when prospective consent is not feasible.

When we contact the individual to obtain prospective informed consent or consent for ongoing data collection, the following options will be provided for study participation:

1. I object to participation in this study including any further contact or data collection.
2. I agree to participation in the study, including data collection regarding medical care given until hospital discharge and agree to be contacted for a follow-up interview.
3. I agree to participation and the ongoing collection of hospital data, but I do not want to be contacted for a follow-up interview.

Paramedics will provide the patient, LAR, or family member with a phone number available 24/7 to contact the study team for additional information on request. This is similar to the process approved by the sIRB and FDA for the PEDI-Dose study of prehospital seizures, also in the PECARN network.

Some study subjects could be emancipated minors less than 18 years of age or otherwise potentially able to provide their own consent. In these cases, we will inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.

When conducting notification and/or consent we will notify the LAR or family member that the patient was in a study, we will review the study goals, medications, and outcomes. We will inform the LAR or family member that participation may be discontinued without penalty of loss of benefits to which the subject is otherwise entitled.

In the event that the research subject dies before notification or consent 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.

Withdrawal:

If an individual declines ongoing participation after being enrolled under EFIC, we will consider this a withdrawal. Once notification of withdrawal is received by the study team, no further data collection will be attempted in accordance with the option selected at the time of signature or verbal consent. 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 drugs.

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 pulmonary clinics, and general pediatrics offices, via the study website, and/or through presentations to professional organizations.

9.4.1 Collection of Mortality and Outcome Data on Eligible Subjects

Since the unit of study intervention is the EMS agency, failure to collect outcome and safety data on all patients treated with the EMS 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 eligibility criteria are considered to be research subjects in this study.

Since all of these patients are either in the intervention (treated under the revised EMS wheezing protocol) or control group (treated under the agency's standard EMS wheezing protocol), all of the patients who meet the eligibility 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 are identified as meeting the eligibility criteria will be exposed to either the intervention or the comparison, notification of enrollment will be provided to the subject, parent/guardian or family member, as appropriate, at the earliest feasible opportunity and an opportunity to object to further data collection will be provided.

Since it is important to ensure that there is no discrepancy in safety between patients transported to the participating EDs and those who are taken to other non-participating 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 (hospital admission status) as long as the study staff have made sufficient efforts to attempt to notify the participant.

This study utilizes a before-and-after design, and the patients who are being treated under the EMS agency's standard wheezing/asthma 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. We will use the same consent process for patients in the control group as the intervention group.

9.4.2 Vulnerable Subjects

Vulnerable populations in this study are children. 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. Also, asthma is the most common chronic illness in children. There is no undue coercion since care received in the prehospital setting will be administered according to patient care protocols/guidelines that are necessarily applied to all patients.

EMS providers are potentially vulnerable as a result of data collected in this study because the data 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-specific information about the care that the paramedics provided.

9.4.3 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.

9.5 Potential Risks

9.5.1 Potential Patient Risks

DuoNeb is a combination of albuterol and ipratropium and will be used in this study, along with Dexamethasone in a bundled treatment protocol. DuoNeb and dexamethasone are widely used medications with favorable side-effect profiles. Adverse effects of DuoNeb are similar in frequency to those of albuterol or ipratropium treatment alone. Some effects listed in the FDA package insert are associated with short-term use of DuoNeb and others are associated with long-term use and therefore not expected to be observed in this study.

Table 6: Potential adverse effects from DuoNeb

Short Term Use	Long Term Use
Changes to pulse rate, blood pressure, and/or other cardiovascular symptoms	Digestive symptoms such as diarrhea, dyspepsia, and nausea
ECG changes	Leg cramps
Allergic-type reactions	Respiratory conditions such as bronchitis, lung disease, pharyngitis, or pneumonia
Bronchospasm, dyspnea, or other respiratory problems	Urinary tract infection (UTI)
Temporary pupil dilation, blurred vision, eye pain, or worsening of narrow-angle glaucoma (if eye exposure)	Constipation and voice alterations
	Unspecified pain and chest pain

Dexamethasone has been used for acute wheezing in children for many years. The FDA package insert lists several adverse effects. These depend on whether the medication is used for a short or long period of time. We do not anticipate long-term adverse effects since we are only giving a single dose.

Table 7: Potential adverse effects from Dexamethasone

Short Term Use	Long Term Use
Abdominal pain (3%) ^{17, 39–42}	Electrolyte disturbances
Nausea or vomiting (1%) ^{17, 39–42}	Blood clots
Behavioral changes (5%) ⁴²	Growth reduction
Allergic-type reactions	Weight gain, malaise, hiccups
	Gastrointestinal, dermatologic, neurologic, endocrine, ophthalmic, metabolic, and cardiovascular complications

Albuterol is already used by all EMS agencies in the study, though enrolled participants may receive more albuterol treatments in the post-intervention phase. Albuterol can cause tachycardia and can also cause shakiness or agitation, additional adverse effects include those previously listed for DuoNeb, as albuterol has a similar side-effect profile.

There is also the risk of loss of privacy for study participants. There is no cost to patients, families, or EMS providers for study participation.

There is some risk a paramedic could enroll an ineligible patient (e.g. with another disease process). In this case, the child would be subject to the risks of the study medications, as described in the previous paragraph. They could also experience discomfort from IM medication delivery that they otherwise would not be subject to.

9.5.2 Potential EMS Provider Risks

We will have demographic information related to some of the EMS providers including their name, age, and experience level as part of the implementation evaluation. EMS providers are not subject to any study intervention so their only risk is loss of confidentiality. We will not report any individual provider-level data to anyone outside of the study team including the employers of the EMS providers.

9.6 Protections Against Potential Risks

Children eligible for this study are cared for by expert pre-hospital paramedic staff who will be following their EMS treatment protocol as prescribed by the medical director. Each agency has oversight from a study investigator who will ensure training is acceptable prior to the start of the intervention.

The minimal risk of loss of privacy is mitigated by the substantial data management resources and security described in [Section 8](#).

9.7 Potential Benefits

Participants in the intervention arm have the potential for direct benefit. We will be applying more aggressive treatment for life-threatening wheezing/asthma than what is currently provided. This has the potential to alleviate symptoms more rapidly, reduce the risk of hospitalization, and improve quality of life.

9.8 Risk Benefit Assessment

Due to the prospect of direct benefit to patients, the risk-benefit ratio is favorable to patients. A 2013 Cochrane review found that combined albuterol ipratropium treatment was superior to albuterol alone for children with acute wheezing as young as 18 months of age and resulted in reduced odds of hospital admission. A 2001 Cochrane review found that early systemic corticosteroids was similarly associated with reduced need for hospital admission among children with acute asthma. A 2012

study by Bhogal et al. found shorter times to steroids were associated with lower hospitalization rates and shorter lengths of time for active treatment. Our study may allow EMS providers to deliver these highly effective treatments significantly earlier than they would be given under the current paradigm, providing earlier relief of life-threatening wheezing/asthma. We will train paramedics on the eligibility criteria to prevent eligibility criteria violations and we will track patients who received the treatment who may have been ineligible.

10 Data and Safety Monitoring Plan

10.1 Study Structure

The study consists of three clinical sites and a Data Coordinating Center (DCC). The sites are Salt Lake City, Buffalo, and Charlotte. Each site will have a site investigator and a research coordinator and will have one or more Emergency Medicine Services (EMS) agencies. The University of Utah will be the Data Coordinating Center. The sites will be responsible for submitting data to the DCC from each EMS agency they are associated with for purposes of the study.

10.2 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB) approved by the funding agency. The DSMB will be composed of a minimum of 3 members. The membership will include representation from experts in the fields of emergency medical services, pediatric emergency medicine with asthma expertise, and biostatistics. The DSMB will have a charter, will approve the protocol prior to enrollment of EFIC participants, and will review interim analyses as applicable. A draft version of the charter has been prepared, which will be finalized before the study begins patient enrollment. The charter will note the responsibilities of the sponsor/investigator, funder, and University of Utah Data Coordinating Center (DCC). The charter will also address the frequency of DSMB meetings, the types of summaries provided in the open and closed sessions, and other pertinent information.

The purpose of the DSMB is to advise the principal investigator(s) and funders regarding the continuing safety of study subjects. The DSMB is responsible for review of serious adverse events and other safety issues.

The DSMB will be expected to meet three times during the study. This will include an initial meeting prior to the start of subject enrollment, one meeting during the active enrollment phase of the study, and once after study completion to review results. If enrollment lasts more than 6 months beyond the first active enrollment meeting, an additional meeting will be held, though this is unexpected given the nature and outcomes of this pilot feasibility study.

10.3 Adverse Event Reporting

10.3.1 Definition of Adverse Event and Serious Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject that occurs during the conduct of a clinical study of a pharmaceutical product that does not necessarily have a causal relationship to the study drug. This can, therefore, be any unfavorable and unintended physical sign, symptom, laboratory parameter, or disease entity that develops or worsens in severity during the course of the study, whether or not considered related to the study drug.

10.3.2 Monitoring Process

We will train research coordinators (RCs) to identify important medical events when they are abstracting study data from the chart or interacting with the medical treatment team during an enrollment visit. Any important events identified by the RC will be brought to the site PI for consideration of AE/SAE reporting. The study goal is to review and report SAEs within 24 hours of medical record availability. Safety outcomes, mortality, ICU admission, and endotracheal intubation rates will be routinely collected and monitored during the study to assess differences between study groups.

The AE monitoring window for this study will begin when the subject receives their first nebulized respiratory treatment or dexamethasone in the EMS setting, or arrival at the hospital, whichever comes first, and will close 24 hours later or upon discharge to home, whichever comes first. This is the window in which any adverse effects of the study treatment bundle would be likely to occur. We will also ask about outcomes in the follow-up communication with parents. Adverse events occurring during EMS care will be captured in the study database, monitored for frequency, and compared between study arms.

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

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires 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.

*One important study outcome in this feasibility study is our ability to collect the hospital admission status from non-affiliated hospitals. We expect that many of the subjects enrolled will be hospitalized

as a result of their baseline condition, so the review of adverse events will focus on new events or the worsening of a baseline condition. We will also compare the rate of hospital admission, regardless of SAE status, between groups to measure any difference in frequency of hospitalization as part of the safety monitoring.

Monitoring for Adverse Events for those who are transferred to a non-affiliated hospital will be limited by the ability to obtain medical records. In the event the record is not obtained, we will collect hospital admission status and a parent report of any problems occurring within 24 hours after EMS care via follow-up.

Unanticipated Problems (UP) We consider unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.3.3 Classification of an Adverse Event (Relatedness, Severity, and Expectedness)

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the criteria below. Relatedness must be assessed by an investigator or designee with equivalent medical and research training.

Not Related: The event is clearly related to other factors, such as the participant’s clinical state, therapeutic interventions, or concomitant drugs administered to the participant.

Possibly Related: The event follows a compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the participant’s clinical state, therapeutic interventions, or concomitant drugs administered to the participant.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot be reasonably explained by other factors such as the participant’s clinical state, therapeutic interventions, or concomitant drugs administered to the participant.

Severity: The severity, which is a measure of intensity, of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. The following guidelines will be used to describe severity.

Mild: The event requires minimal or no treatment and does not interfere with the participant's daily activities.

Moderate: The event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: The event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

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 the risk information described for the study intervention or the condition under study.

Expected: An event is considered expected if it is known to be associated with the underlying condition or is related to the study intervention and is mentioned in the protocol, informed consent, or other study documents. An event may be expected despite the study participant'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 condition or intervention under study or an event that occurred unexpectedly in the course of treatment.

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

- 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 permanent sequelae
- Symptoms persist beyond hospital discharge (ongoing)

10.3.4 Collection and reporting of AEs and SAEs

Adverse events (including all serious adverse events) will be recorded according to relatedness, severity, and expectedness, as well as their duration and any treatment prescribed. Any medical condition present before albuterol is administered, which remains unchanged or improves (unless the clinician feels it is clinically relevant), will not be recorded as an adverse event at subsequent evaluations. However, new or worsening medical condition(s) will be collected.

Research coordinators will report AEs to the site PIs. AE identification will be through medical record review of the prehospital and hospital records, and for patients discharged within 24 hours, will include events identified through follow-up texts/phone calls. The research coordinators at each site will be responsible for reporting potential AEs to the site investigator who will determine the AE status; if deemed an AE, the site investigator will determine seriousness, relatedness, and expectedness. All SAEs will be reported to the DCC within 24 hours of the site becoming aware of the event and will be followed until resolution or hospital discharge (if ongoing). If an AE is serious, unexpected, and related, it will be reported to the IRB as required by IRB reporting policies. The IRB may subsequently report to other regulatory agencies such as the FDA and NIH as per the reporting policies of these agencies.

All AEs will be reported by the sites to the DCC using the electronic data capture system. Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center as this requires specific training. AE frequency will be monitored by the DSMB during the interim and study completion meetings and by each event will be reviewed by the Medical Monitor during the duration of enrollment.

10.3.5 SAE and UP Event Reporting Timelines

10.3.6 Reporting and Monitoring Unanticipated Problems

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related or possibly related to participation in the study, and suggest that the research places participants at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the single IRB (sIRB) in an expedited manner (as close to 24 hours as possible). If the sIRB agrees the event is a UP, the DCC will also report to NHLBI in an expedited manner. In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the Data Coordinating Center. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NHLBI cannot be reached expeditiously, the DCC will notify the study principal investigator (Dr. Hansen) and all site investigators to cease data collection or to stop using a particular medication as appropriate based on the nature of the unanticipated problem. Resumption of enrollment will not occur without consent of the NHLBI.

Table 8: SAE and UP Event Reporting Timelines

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Reporting goal of 24 hours after initial receipt of information	Investigator	EMSC Data Center (EDC)
-	Within 7 calendar days of initial receipt of information	EMSC Data Center (EDC)	FDA
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Reporting goal of 24 hours after initial receipt of information	Investigator	EMSC Data Center (EDC)
-	Within 15 calendar days of initial receipt of information	EMSC Data Center (EDC)	FDA (IND/Marketed Products) All participating investigators
Unanticipated Problem that is not an SAE	Within 14 days of the investigator becoming aware of the problem	Investigator	EMSC Data Center (EDC)
All Unanticipated Problems ²	Within 30 days of the IRB's receipt of the report of the UP from the investigator.	IRB Investigator	OHRP External IRBs

10.3.7 FDA Reporting

The PI will prepare an IND safety report for any potential serious and unexpected adverse reactions according to FDA regulations and definitions.

10.3.8 Monitoring Serious Adverse Events

A qualified physician will be designated to fulfill the function of the medical monitor for this study. The medical monitor will be appointed by the DCC and will be independent from the study and DSMB. Medical monitors are typically University of Utah faculty physicians who work closely with the DCC, but are not affiliated with the study other than to fulfill the medical monitor role. The medical site investigators and/or research coordinators will report serious adverse events to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC 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 the continuation of the trial. The medical monitor will sign off on each SAE report after review. All SAE reports will be retained at the DCC, and all SAE reports will be available for review by DSMB members and the NHLBI. The SAE reporting process will 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, NHLBI and the DSMB chair will be immediately consulted. If they concur with the judgment of the medical monitor, or if the NHLBI and DSMB chair cannot be reached expeditiously, the DCC will notify the study principal investigator (Dr. Hansen) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI after discussion with the medical monitor and DSMB chair.

This is not an efficacy study but is a pilot study with a short enrollment period for the intervention phase. Given there are no formal interim analyses, there are no formal stopping rules for the trial.

After notification of the IRB, NHLBI, DSMB chair, and the medical monitor of serious, unexpected, and study-related adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Hansen) and all clinical investigators, who will be instructed to report this to their local IRB.

The medical monitor will review all adverse events (not necessarily serious, unexpected, and study-related).

10.4 Reporting mechanisms for changes or amendments to the protocol or consent form

All changes to the study protocol and consent form will be approved by the central IRB. Any such changes that impact the risk of the study will be reported promptly to NHLBI.

10.5 IND Information

Before the study enrollment period begins, an IND application from FDA will be obtained for the albuterol/ipratropium nebulizer and dexamethasone since they are not FDA-approved for pediatric wheezing and since this is an EFIC study.

10.6 Data Collection

10.6.1 Data Acquisition

Types of data collection are described in greater detail in Sections 6–6.5 of the protocol. Pre-hospital data will be gathered by EMS agencies and transferred to the University of Utah Data Coordinating Center (DCC). Research assistants will obtain access to the medical records as allowable and abstract the study's data elements into the DCC-maintained EDC system. Hospital data will be abstracted from medical records. For PECARN hospitals, research coordinators will directly enter data into the study's EDC. For community hospitals, possible methods may include but are not

limited to establishing a direct portal into the electronic health record to abstract hospital data, traveling to local hospitals to use an on-site portal to the medical record, or using a community hospital data abstractor if available. For emergency department screening data, the EHR and/or screening protocols will be used to identify eligible patients. Follow-up data from the patient or parent proxy will be collected through an automated system, using text messages as used by the DCC in other studies and followed up with a phone call from the research coordinator if needed.

10.6.2 Study data collection monitoring

Given the short duration of the study, we will evaluate the number of enrollments and general adherence to the study protocol on a twice-monthly basis, especially during the intervention phase. This will allow us to investigate potential causes of protocol adherence problems, reinforce the protocol, provide additional just-in-time education, and improve adherence during the short 5-month intervention window.

10.7 Data Analysis Plans

See section 3.7.6 in the grant for the analysis plan, which will be further described in a Statistical Analysis Plan. In brief, Aim 2 pertains to the feasibility of collecting study outcomes, and we will summarize the proportion of enrolled patients for whom the primary outcome is collected, overall, and by site. We will similarly summarize the secondary outcome. We will construct one-sided 95% exact binomial confidence intervals for each such proportion, overall and by site, to provide the interval's lower bound for each capture proportion. The lower bounds will be useful to gauge the relative feasibility of using hospitalization or the PROMIS asthma impact score as a primary outcome in the future trial. To account for missing data that are not necessarily missing completely at random, statistical analyses may use multiple imputation approaches.

10.7.1 Interim data analysis

There are no formal interim efficacy analyses (e.g., to permit stopping the study early for efficacy or futility). This is a pilot trial to demonstrate the feasibility of collecting the study outcomes. This study was not powered to demonstrate the efficacy of the treatment bundle, but rather the feasibility of data collection, and protocol adherence. Limited information will be available to compare the treatment bundle with the intervention phase during the study given that the active enrollment phase is planned to last five months. Interim safety analyses will be comprised of the data summaries presented to the DSMB, and the DSMB has the right to recommend early termination of the study based on interim data review without needing formal data rules to automatically trigger study termination. If data completion or protocol adherence rates are worse than anticipated, we prefer to allow the study to continue to see if the rates can be improved sufficiently to justify a larger trial.

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 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 investigator Dr. Hansen, will be the main contact for study questions.

12 Regulatory Considerations

12.1 Food and Drug Administration

The study medications are not FDA approved for children, despite regular off-label use as a standard of care, therefore an IND will be required from the FDA.

12.2 Health Insurance Portability and Accountability Act

Some data elements collected in the study include PHI including dates of birth and dates of service and may include some limited linkage identifiers such as MRN or EMS run number. These data will be limited to the minimum necessary to achieve the objectives of the study. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude these specific dates.

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 research data sets that will be used for analyses, all study sites will be 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 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

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 §)

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