Pediatric Prehospital Airway Resuscitation Trial (Pedi-PART)
PECARN Protocol Number 057

Pediatric Emergency Care Applied Research Network
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PROTOCOL TITLE:

Pediatric Prehospital Airway Resuscitation Trial

Short Title: Pedi-PART
PECARN Protocol Number: 057

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Ohio State 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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Abstract

Cardiac arrest, respiratory failure, and major trauma are devastating critical conditions in children. Resuscitation from critical illness requires skillful airway management to optimize the delivery of oxygen to the lungs, preventing irreparable damage to the brain and heart. As the first to provide resuscitation care for critically ill children, prehospital EMS personnel are often the first to perform life-saving airway management.

The most common prehospital airway management techniques (bag-valve-mask ventilation [BVM], endotracheal intubation [ETI], and supraglottic airway insertion [SGA]) have important trade-offs between risks and benefits. Despite the challenges of ETI and national recommendations favoring BVM, many EMS personnel favor ETI over BVM. Newer SGA devices such as the laryngeal tube (LT), laryngeal mask airway (LMA), and i-gel® have not been compared with other techniques in children. National organizations, including the Agency for Healthcare Research and Quality, have declared the need for new, rigorous trials of all techniques to determine the best strategies for prehospital airway management in children. Interviews with front-line EMS personnel underscore the dire need for clear and strategic guidelines for managing the pediatric airway.

The Pediatric Prehospital Airway Resuscitation Trial (Pedi-PART) will determine the best strategies for prehospital airway management in critically ill children. The trial aims are **Aim I-Primary Objective** (Effectiveness)-Stage I: Determine if [BVM-only] or [BVM followed by SGA] results in better ICU-free survival in critically ill children with cardiac arrest, major trauma, or respiratory failure. Stage II: Determine if [Winner of Stage I] or [BVM followed by ETI] results in better ICU-free survival. Bayesian analyses will determine the transition from Stage I to Stage II, ensuring optimal deployment of available subjects to address the postulated questions. **Aim 2- Secondary Objective** (Safety)- Stage I: Determine if [BVM followed by SGA] results in fewer prehospital and hospital safety events compared with [BVM-only] in critically ill children with cardiac arrest, major trauma, or respiratory failure. Stage II: Determine if the Winner of Stage I results in fewer safety events compared with [BVM followed by ETI].

The trial will use a Bayesian Adaptive Sequential Comparison Platform Trial (BASiC-PT) design and will be executed in two sequential stages. Stage I: Determine if [BVM-only] or [BVM followed by SGA] results in better ICU-free survival in critically ill children with cardiac arrest, major trauma, or respiratory failure. Stage II: Determine if [Winner of Stage I] or [BVM followed by ETI] results in better ICU-free survival. Bayesian analyses will determine the transition from Stage I to Stage II, ensuring optimal deployment of available subjects to address the postulated questions.

1 Abbreviations

Abbreviation	Definition
AE	Adverse Events

BASiC-PT	Bayesian Adaptive Sequential Comparison Platform Trial
BiPAP	Bi-level Positive Airway Pressure
BVM	Bag Valve Mask
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
DCC	Data Coordinating Center
EDC	Electronic Data Capture
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
EFIC	Exception From Informed Consent
EMS	Emergency Medical Services
ETI	Endotracheal Intubation
ETT	Endotracheal Tube
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
HIPAA	Health Information Portability and Accountability Act
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IM	Intramuscular
IN	Intranasal
IO	Intraosseous
ITT	Intent-To-Treat Population
IV	Intravenous
LCP	Liquid Cooling Package
LMA	Laryngeal Mask Airway
LT	Laryngeal Tube
MedDRA	Medical Dictionary for Regulatory Activities
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
PCPC	Pediatric Cerebral Performance Category score
PECARN	Pediatric Emergency Care Applied Research Network
PI	Principal Investigator
PP	Per-Protocol Population
PR	Rectal
RSI	Rapid Sequence Intubation
SAE	(Serious) Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGA	Supraglottic Airway
TLS	Transport layer security

VL	Video Laryngoscopy
VPN	Virtual private network

2 Study Summary

This study is a Phase 3, multi-center, Bayesian Adaptive Sequential Platform Trial testing the effectiveness of different prehospital airway management strategies in the care of critically ill children. EMS agencies from 10 sites across the country will participate in the trial. The study interventions are strategies of prehospital airway management: [BVM-only], [BVM followed by SGA] and [BVM followed by ETI]. The primary outcome is 30-day ICU-free survival. The trial will be organized and executed in two successive stages. In Stage I of the trial, EMS personnel will alternate between two strategies: [BVM-only] or [BVM followed by SGA]. The [Winner of Stage I] will advance to Stage II based upon results of Bayesian interim analyses. In Stage II of the trial, EMS personnel will alternate between [BVM followed by ETI] vs. [Winner of Stage I].

2.1 Study Objective and Outcomes

Aim 1 – Primary Objective (Effectiveness) – Stage I: Determine if [BVM-only] or [BVM followed by SGA] results in better ICU-free survival in critically ill children with cardiac arrest, major trauma, or respiratory failure. Stage II: Determine if [Winner of Stage I] or [BVM followed by ETI] results in better ICU-free survival. Bayesian analyses will determine the transition from Stage I to Stage II, ensuring optimal deployment of available subjects to address the postulated questions.

Aim 2 – Secondary Objective (Safety) – Stage I: Determine if [BVM followed by SGA] results in fewer prehospital and hospital safety events compared with [BVM-only] in critically ill children with cardiac arrest, major trauma, or respiratory failure. Stage II: Determine if the [Winner of Stage I] results in fewer safety events compared with [BVM followed by ETI].

2.2 Primary Outcome

The primary outcome is 30-day ICU-free survival.

2.3 Secondary Outcomes

The main secondary outcome is neurologic outcome on hospital discharge, measured with the widely used Pediatric Cerebral Performance Category score (PCPC – 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, 6 = dead).[1]

2.4 Safety Outcomes

Additional safety outcomes will include:

- Procedural events (unsuccessful advanced airway management, multiple [≥ 3] advanced airway insertion attempts, airway misplacement or dislodgement).
- Physiological events during or after airway management efforts (oxygen de-saturation [decrease to SpO2 < 80%], hypotension [SBP decrease to < 5th age percentile], bradycardia [heart rate decrease < 60 beats/minute], cardiac arrest, vomiting/regurgitation, airway injury [laceration, bleeding, etc], pneumothorax, pneumonia/pneumonitis, death).

3 Rationale and Background

Out-of-hospital pediatric cardiac arrest, trauma, and respiratory failure are important public health problems. At least 15,000 children suffer an out-of-hospital cardiopulmonary arrest (OHCA) each year in the US. The low survival rate of 8.3% in pediatric OHCA patients combined with the knowledge that hundreds of thousands of children suffer traumatic injury and respiratory failure due to a variety of causes underscores the dramatic need for improved prehospital interventions.[2–7]

Airway management is a key element for successful resuscitation. The goal of airway management is to optimize outcomes by controlling oxygen delivery and ventilation and preventing gastric aspiration.[8] Optimal delivery of oxygen to all vital organs is especially important for children due to their high metabolic rate, limited physiologic capacity, and lower lung capacity. Critically ill patients are also prone to aspirating gastric contents.

The fundamental technique for prehospital airway management is bag-valve-mask ventilation (BVM). However, EMS personnel often perform the more advanced technique endotracheal intubation (ETI or "intubation"), which involves opening the mouth using a lighted metal laryngoscope blade and guiding a plastic breathing tube between the vocal cords into the trachea. A third newer technique is the supraglottic airway (SGA); examples include the laryngeal tube (LT), laryngeal mask airway (LMA), and the i-gel®. SGAs are inserted blindly through the mouth, sit outside the vocal cords, and deliver oxygen indirectly into the trachea. SGA devices are typically easier and faster to place and require less skill and training compared to ETI.[9]

Numerous studies highlight the pitfalls and trade-offs of EMS personnel airway management techniques. BVM often requires two operators and may fill the stomach with air, increasing the risk of regurgitation and aspiration.[10, 11] ETI is highly complex; its potentially lethal pitfalls include oxygen deprivation from multiple failed insertion attempts and unrecognized tube misplacement, oropharyngeal injury, and interference with concurrent treatments such as CPR chest compressions.[12–17] EMS personnel training and clinical experience are often inadequate to maintain ETI proficiency.[12, 18–21] In many systems, EMS personnel intubate a child only once every five years.[22] Newer SGAs are easy to learn and use, deliver ventilation similarly to ETI, and demonstrate equal or better outcomes than ETI in adult OHCA.[23–25] However, the efficacy of SGA over ETI is unproven in children.[24, 26]

Existing studies have major limitations. National organizations – including the Agency for Healthcare Research and Quality and the National Association of Emergency Medical Services Physicians – have singled out the need for rigorous randomized controlled trials comparing prehospital BVM, ETI, and SGA in children.[27] Understanding airway management in children is important because: 1) the etiology of respiratory failure in children differs from adults, and 2) the distinctions of pediatric airway anatomy often render airway management more difficult. There is a paucity of data with sufficient rigor to guide prehospital airway management practices in children. In a systematic review, there were only eight studies of pediatric prehospital airway management. Gausche-Hill's study of 830 critically ill children in Los Angeles remains the only clinical trial of prehospital pediatric airway interventions.[28]

The strongest evidence of clinical equipoise is the wide variation in pediatric prehospital airway practices currently in use. While national guidelines recommend prehospital BVM in critically ill children, in current practice EMS personnel use a combination of BVM, ETI and SGA.[28] Analyses of the national Cardiac Arrest to Enhance Survival (CARES) and the National Emergency Medical Service Information System (NEMSIS) affirm the current wide varying use of BVM (45–54%), ETI (42–49%), and SGA (1–13%).[29–31] Two major factors likely drive the variation in EMS personnel pediatric airway practices. First, EMS personnel in many communities remain reluctant to give up pediatric ETI. Key criticisms of the Gausche-Hill clinical trial include its age (> 20y ago) and EMS personnel's lack of experience with ETI.[28] Over half of surveyed EMS medical directors indicated "more evidence is needed" or "[the results of the Gausche trial] do not apply to my EMS system" as top reasons to continue prehospital pediatric ETI.[32] Second, newer SGA devices are now available for prehospital use in children; however, their use is extrapolated from adult trials with little supporting pediatric data.[9, 33, 34] The variation in current practice indicates that new data are needed to identify the best prehospital airway management techniques in critically ill children.

4 Setting

The trial will be carried out by EMS agencies associated with the Pediatric Emergency Care Applied Research Network (PECARN).

5 Subject Eligibility, Accrual and Study Duration

5.1 Eligibility criteria

Inclusion criteria are:

- At least 24 hours old and < 18 years old
- Cardiopulmonary arrest, major trauma or respiratory failure
- Life-saving care initiated or continued by Pedi-PART EMS personnel as part of an emergency "9-1-1" response

- Requiring active airway management (BVM or higher level of respiratory support)

Exclusion criteria are:

- Prisoners
- Pre-existing tracheostomy
- Pre-existing do-not-resuscitate/do-not-intubate status
- Visibly or known to be pregnant
- Initial advanced airway attempt by an EMS agency not affiliated with the study
- Interfacility transports

EMS personnel will use bystander reports or follow local protocols to establish patient age, and pregnancy status.

5.2 Subject Accrual and Study Duration

Subject accrual will occur over an approximately 5-year period. Across Stages I and II, the trial will enroll approximately 3,000 subjects.

6 Study Procedures

6.1 Overview of the Adaptive Platform Trial Design

The trial uses a Bayesian Adaptive Sequential Platform Trial (BASIC-PT) framework. (Figure 1) The study interventions are strategies of prehospital airway management: [BVM-only], [BVM followed by SGA] and [BVM followed by ETI]. The primary outcome is 30-day ICU-free survival.

The trial will be organized and executed in two successive stages. In Stage I of the trial, EMS personnel will alternate between two strategies: [BVM-only] or [BVM followed by SGA]. The [Winner of Stage I] will advance to Stage II based upon results of Bayesian interim analyses. In Stage II of the trial, EMS personnel will alternate between [BVM followed by ETI] vs. [Winner of Stage I].

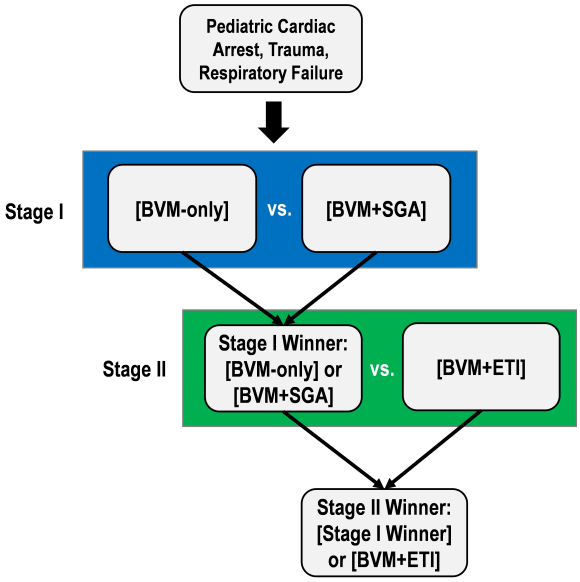

Figure 1: Overview of the Trial. Stage I will compare [BVM-only] vs. [BVM followed by SGA [BVM+SGA]], enrolling subjects until there is a "winner." Stage II will then compare the [Winner of Stage I] vs. [BVM followed by ETI [BVM+ETI]].

6.2 Identification of Patients

EMS personnel will identify eligible patients during the course of clinical care. Identification of eligible subjects will occur at all times of the day and on all dates.

Research teams will identify enrolled subjects through a range of mechanisms such as:

- Screening of receiving Emergency Departments for EMS arrivals.
- Receipt of notification by EMS personnel via phone, e-mail or other messaging system.
- Review of EMS care logs.

6.3 Study Interventions

The study intervention is the initial strategy of prehospital airway management:

- BVM-only
- BVM followed by ETI [BVM+ETI]
- BVM followed by SGA [BVM+SGA].

The trial postulates that different airway management strategies elicit improved outcomes by altering the organization or choreography of resuscitation care. For example, in the PART trial, the SGA strategy resulted in 2.7 minutes faster airway insertion than ETI.[24]

The normal clinical course of advanced airway management consists of initial BVM followed by

progression to SGA or ETI when clinically appropriate; this is the rationale for denoting [SGA] as [BVM+SGA], and [ETI] as [BVM+ETI]. When caring for an apneic patient, EMS personnel initiate airway care with BVM, later transitioning to SGA or ETI when equipment are prepared and conditions are optimal; for example, during a pause in CPR chest compressions. There are instances where BVM use may be transient, or when the EMS crew may arrive at the hospital before SGA/ETI can be accomplished; these are normal outcomes and would be retained in the assigned intention-to-treat group. In PART and Airways-2, among patients assigned to ETI or SGA, BVM-only use occurred in up to 17% of cases.[24, 26] If BVM is in progress prior to EMS arrival, the patient will be included in the trial.

If the initial airway management strategy is unsuccessful, EMS personnel may rescue with any available airway management technique. EMS personnel may also deviate from the assigned strategy to ensure patient safety; for example, to protect the airway in the case of active vomiting.

SGA and ETI subtypes

SGA will include the EMS agency's customary device: for example, laryngeal tube (LT), laryngeal mask airway (LMA) or i-gel®. In current practice, most EMS agencies use the i-gel SGA.

ETI will include all intubation techniques available to the EMS agency, including rapid sequence intubation (RSI) and video laryngoscopy (VL).

If SGA or ETI attempts are unsuccessful or if there is a patient threat (e.g., vomiting), EMS personnel may rescue with any available airway technique.

Transitions between stages – Stage I and II "winners"

The trial will be organized and executed in two successive stages so that only two interventions are compared at a given time: Stage I [BVM-only] vs. [BVM+SGA], and Stage II [Winner of Stage I] vs. [BVM+ETI]. The transition from Stage I to Stage II will be based upon results of Bayesian interim analyses. The definitions of superiority and inferiority are based upon the perceived relative complexity of each airway strategy.

- **Stage I:** EMS rescuers view BVM as more complex than SGA. BVM requires continuous maintenance of a mask seal, and optimal operation may require two rescuers.[35] In contrast, SGAs are relatively easy to insert and do not require continuous efforts to maintain a seal.[36] Therefore, since SGA is less complex than BVM, [BVM+SGA] will advance to Stage II if it proves noninferior to [BVM-only]. [BVM-only] will advance to Stage II only if it demonstrates superiority to [BVM+SGA].
- **Stage II:** ETI is more complex than BVM and SGA.[11] Therefore, in Stage II, [BVM+ETI] will be declared the winner if it demonstrates superiority to [winner of stage I]. [Winner of Stage I] will be declared the winner if it demonstrates non-inferiority to [BVM+ETI].

6.4 Allocation of Interventions

We will allocate patients to airway management strategy using an approach based upon odd/even calendar date. For example, in Stage I allocation may proceed as: odd-numbered day = [BVM+SGA],

even-numbered day = [BVM-only]. For the 31st and 1st day of the month, EMS personnel would stay on [BVM+SGA].

Adjustments will be made to the odd/even allocation strategy to accommodate operational requirements. For example, instead of the calendar date and time, the allocation strategy may alternate based upon the start of the EMS personnel's 24-hour work shift (typically 6 or 7 AM). For example, for a work shift starting at 7 AM January 1, paramedics would perform [BVM+SGA] for all cases during the 24-hour work period, including patients encountered between midnight and 6:59 AM on January 2. The same allocation principles will be applied to the Stage II interventions.

7 Data Collection

7.1 Data Variables

Data variables that will be collected may include but not be limited to:

- Incident dates and times
- Response characteristics
- Incident type
- Patient demographics
- Patient prior medical history
- Vital signs and cardiac rhythm
- Prehospital airway interventions
- Other prehospital treatments and medications
- Prehospital outcomes
- Hospital course
- Hospital outcomes
- Readmissions within 30 days
- Safety events
- Notification of family members or legally authorized representative
- Cardiac monitor files

7.2 Data Sources

Sources of data to be collected for all enrolled subjects include:

- Prehospital Data from EMS electronic health record, EMS personnel self-reports, and cardiac monitor files
- Hospital Data including clinical and safety outcomes.

Where available, publicly available data such as public death records may be used to augment other records.

At the time of notification of enrollment in the trial (see Section 11.2.1), participants and parents/guardians will have the option to continue or withdraw from further data collection. If a participant is withdrawn from further data collection, no data will be collected after the date/time of the participant withdrawal. If notification of trial enrollment is not successful, participant data will be collected as described above.

EMS personnel document the majority of prehospital care in the EMS agency's electronic medical record. Where research teams do not have direct access to EMS electronic medical record data, EMS agencies will regularly and securely transfer data to the study team. Additional study-related data may be reported by EMS personnel through other methods (e.g., direct interview by research personnel at receiving EDs, phone notification to research personnel, completion of on-line data collection forms, completion of supplemental paper data forms).

EMS and hospital records will be linked at the hospital based upon patient identifiers such as last name, first name, destination of transport, date of birth and date/time of ED arrival. Research teams will attempt to collect hospital records for all patients enrolled in the study, regardless of the destination of transport. Research teams have an existing relationship with the Children's hospitals at their site, where the majority of patients will be transported, and will work to establish relationships with other hospitals in order to obtain records.

Abstracted research data will be entered into a secure electronic database that is housed at the PECARN Data Coordinating Center (DCC), based at the University of Utah.

8 Statistical Summary

8.1 Overview

Full details of the statistical analysis are provided in the separate Statistical Analysis Plan (SAP).

Under the novel BASiC-PT framework, Bayesian adaptive methods will be used to conduct sequential pairwise comparisons between different airway management strategies with pre-defined superiority and non-inferiority criteria set for each comparison between phases of the study (Figure 2). Stage I will be executed until Bayesian interim analyses determine a "winner" between the Stage I interventions ([BVM-only] and [BVM+SGA]). The trial will then transition to Stage II, which will enroll subjects until Bayesian interim analyses determine a "winner" between the Stage II interventions ([Winner of Stage I] and [BVM+ETI]).

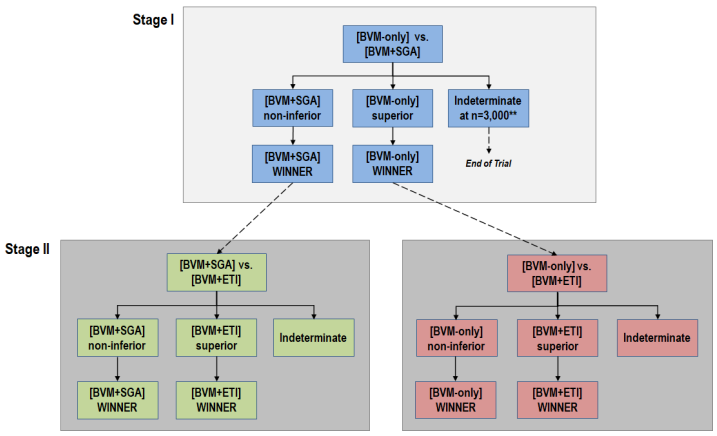

Figure 2: Potential Outcomes of the Trial. Overview of group comparisons and potential transitions from Stage I to II. If Stage I enrolls the full cohort ($n = 3,000$) but the result is indeterminate, then the trial will end.

The data will be analyzed by intention-to-treat. Sensitivity analyses will be performed using the per-protocol population. The primary focus of the hierarchical models is upon the overall treatment effects of the different airway strategies (e.g., [BVM-only] vs. [BVM+SGA], [BVM-only] vs. [BVM+ETI], [BVM+SGA] vs. [BVM+ETI]), adjusting for varying disease group, age, and site; the latter are confounders and are not the focus of the analysis. This approach is consistent with the overarching goal of efficiently answering the highest priority scientific hypotheses while accounting for potentially important contributors.

8.2 Data Analyses

8.2.1 Study Outcomes

The primary outcome is 30-day ICU-free survival, defined as the number days in the first thirty-days after ED arrival where: 1) the patient was not known to have died; and 2) the patient was not hospitalized in the intensive care unit.[37, 38] ICU admission/discharge criteria will not be standardized.

The main secondary outcome is neurologic outcome upon hospital discharge, measured with Pediatric Cerebral Performance Category score (PCPC – 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, 6 = dead).[1]

8.2.2 Primary Analyses

For Stage I, [BVM+SGA] vs. [BVM-only], we will use a Bayesian hierarchical linear model that adjusts for disease state, age group, and site to estimate global treatment effects by airway management technique. We will determine the effect of airway strategy ([BVM-only] vs. [BVM+SGA])

upon a patient-centered score of 30-day ICU-free survival accounting for disease state, age group and site. We will conduct sequential pairwise comparisons between different airway management strategies with pre-specified criteria.

The hierarchical modeling approach will allow us to compare airway management strategies overall and quantify treatment effects within the three disease states: 1) cardiac arrest, 2) major trauma, and 3) respiratory failure, as well as across various age groups. All data will be analyzed by the intention-to-treat principles. The results will be expressed in terms of Bayesian posterior probabilities which indicate the probability of the observed effect.[39] The analysis will use non-informative prior probabilities in the Bayesian hierarchical modeling. We verified one-sided 2.5% Type I error control via simulation. The posterior probability cutoff of 97.5% defining statistical significance is based on these simulations.

The adaptive decision to progress from Stage I to Stage II will be based on interim analyses of the overall treatment effect which will be performed after every 300 patients are enrolled.

The analysis of Stage II, [Winner of Stage I] vs. [BVM+ETI], will proceed similarly to Stage I. We will conduct sequential pairwise comparisons between different airway management strategies with pre-specified success criteria. Because ETI is the more complex procedure, [BVM+ETI] must demonstrate superiority over [Winner of Stage I] to be declared the [Winner of Stage II]. Conversely, since BVM and SGA are easier than ETI, [Winner of Stage I] must demonstrate non-inferiority to [BVM+ETI] to be declared the [Winner of Stage II].

8.2.3 Subgroup Analyses

Analysis of major subgroups will be analyzed in much the same manner as the primary outcomes. (Table 1) The primary analysis will be performed by intention-to-treat. We will conduct additional per-protocol and as-treated analyses. Additional secondary subgroup analyses may include: race, ethnicity, and transportation time ($\leq$ 15 vs. $>$ 15 minutes).

Table 1: Major Subgroup Analyses

Subgroup	Analyses
Cardiac arrest	Initial Rhythm (shockable vs. non-shockable)
Major Trauma	Mechanism of injury (blunt vs. penetrating vs. burn)
	Hypotension/Shock (initial SBP below age threshold)
Respiratory Failure	Sepsis, Drug overdose, Seizures, asthma and related conditions
	Hypotension/Shock (initial SBP below age threshold)
Age Groups	Infant < 1 year, toddler and pre-school 1–5 years,
	child 6–12 years, adolescent 13–17 years

8.2.4 Safety Outcomes

The trial will evaluate airway related safety endpoints that may result from all of the studied airway strategies ([BVM-only], [BVM+SGA], [BVM+ETI]), including events in the prehospital setting, the Emergency Department (ED), and subsequent hospital course (Table 2). Airway management can cause physiologic changes such as hypotension, bradycardia, and cardiac arrest. Excessive attempts at intubation are also associated with hypoxia and cardiac arrest.[40] Emergency Department information may indicate prehospital safety events such as unrecognized esophageal intubation, mainstem intubation, airway injury, pneumothorax, etc. Subsequently, we will evaluate for the presence of pneumonia/pneumonitis and death. In prior studies, we found that children treated with prehospital ETI had significantly higher odds of pneumonia compared to those treated with BVM.[41] Research teams will ascertain safety endpoints by review of medical records.[24] We will create procedures detailing the methods for identification of these events from the medical record. Research staff will undergo structured training in the application of these methods.

Table 2: Safety Endpoints

Source	Physiologic Safety Events	Procedural Safety Events
Prehospital Records	During or after airway management: • Oxygen de-saturation (decrease to SpO2 < 80%) • Hypotension (SBP decrease to < 5th age percentile) • Bradycardia (< 60 beats/minute) • Cardiac arrest • Vomiting/regurgitation • Airway injury (laceration, bleeding, etc) • Death	• Unsuccessful advanced airway management • Multiple (≥ 3) advanced airway insertion attempts • Airway misplacement or dislodgement
ED Records	• Airway injury (laceration, bleeding, hypopharyngeal/gastric perforation, etc) within 1 hour of ED arrival • Pneumothorax on initial radiology interpretation of chest X-ray or chest CT within 1 hour of ED arrival • Pneumonia/pneumonitis from radiology interpretation of chest x-rays or chest CTs within 72 hours of ED arrival • Death	• EMS airway misplacement or dislodgement
In-patient Records	• Pneumonia/pneumonitis (from radiology interpretation of chest x-rays within 72 hours of ED arrival) • Death	

8.2.5 Interim Monitoring

Under the Bayesian adaptive framework of the trial, interim analyses will be conducted after every 300 patients are enrolled.

8.2.6 Missing Data

Per the intention-to-treat principle, subjects who withdraw from the study or are lost to follow-up will have all available data used in the analysis. In the event that a substantial number of subjects are withdrawn or lost to follow-up, baseline characteristics and available information on hospital

course will be reviewed and compared to subjects not withdrawn or lost, to assess empirically if these subjects differ from those remaining in the study for the scheduled treatment and follow-up time.

The outcomes are collected from the time of prehospital care and the hospital stay and will not require patient follow up beyond the hospital stay. Due to the ability to find the outcomes in the electronic health record, we anticipate very low missing rates for primary and secondary analyses. For this reason, the primary and secondary analyses will use complete case analyses if there are minimal missing data. If the rate of missing data is > 10%, we will consider using multiple imputation using sequential regression methods to perform the analyses.

8.2.7 Populations for Analyses

The primary analysis will be conducted by Intention-To-Treat (ITT) principles and will include all patients enrolled in the study. The per-protocol population will be used for sensitivity analyses.

Outcomes data may not be available for the rare instance where the child is transported to a hospital not affiliated with the study. For example, a child in cardiac arrest may be transported to the nearest community hospital rather than the regional children's hospital. Every attempt will be made to obtain the medical record for these patients in order to provide outcomes for the study.

8.3 Sample Size Justification

Full details of the sample size and Bayesian simulations are provided in the Statistical Analysis Plan. We project capacity to enroll 3,000 critically ill and injured children requiring airway management over a 4–5 years enrollment period. Under the efficient BASiC-PT design framework, this sample size is sufficient to detect meaningful differences in ICU-free days between [BVM-only] and [BVM+SGA], accounting for the expected differences in the three disease groups. This also takes into account the minimum meaningful differences ascertained from our preliminary data.[42]

Simulation results support the maximum sample size. (Table 3) Leveraging data from the Los Angeles County Pediatric Airway Trial, we simulated pediatric 30-day ICU-free outcomes for: 1) cardiac arrest, 2) major trauma, and 3) other respiratory failure.[37] We derived operating characteristics for Stage I of the Pedi-PART trial, comparing 30-day ICU-free outcomes in BVM and SGA using our Bayesian hierarchical model, where the treatment effect, Θ, roughly corresponds to the change in expected utility score between the two arms. We simulated 5,000 trials for each of the null scenarios, and 1,000 trials for each of the alternative scenarios.

Table 3: Operating Characteristics of the Trial. Overall operating characteristics for each scenario in Stage I, including average sample size for Stage I, the probability of declaring superiority in Stage I, and the probability of declaring non-inferiority in Stage I. Θ = Difference in expected utility score. Full details are in the Statistical Analysis Plan.

Scenario	Treatment Effect (Θ)	Better Arm	Average Sample Size	Probability [BVM-only] Superior to [BVM+SGA]	Probability [BVM+SGA] Non-inferior to [BVM-only]
1	−1.25	[BVM+SGA]	909	**0.000**	**0.976**
2	−0.75	[BVM+SGA]	1,496	**0.004**	**0.827**
3	0.00	–	2,615	**0.016**	**0.195**
4	0.75	[BVM-only]	2,555	**0.235**	**0.016**
5	1.25	[BVM-only]	1,822	**0.700**	**0.002**
6	1.50	[BVM-only]	1,351	**0.877**	**0.003**

Allocation of subjects between Stages I and II

The total pool of 3,000 enrolled patients is the maximum that can be studied with the available resources. While the initial target enrollment is 1,500 in each of Stages I and II, the actual allocation between stages is adaptive and will be based upon interim Bayesian analyses. Patients will be enrolled in Stage I until 1) the trial declares a Stage I "winner" or 2) the maximum sample size of 3,000 has been enrolled. If a definitive Stage I answer is reached prior to 1,500 subjects, then the remaining patients will be reallocated to Stage II. If a definitive result is not reached by 1,500 subjects, then Stage I will continue enrolling subjects until the trial yields a Stage I "winner." If all 3,000 patients are needed to answer Stage I, then the trial will not proceed to Stage II; this scenario is acceptable, reflecting dedication of resource to the highest priority comparison ([BVM-only] vs. [BVM+SGA]).

Minimum number of subjects needed for Stage II

Power simulations support that $n = 500$ is the minimum sample size needed for Stage II to yield clinically useful results. Therefore, if Stage I enrolled > 2,500 subjects, we would not transition to Stage II. An alternative to canceling Stage II would be to enroll patients in Stage II using a 2:1 or 3:1 [BVM+ETI]:[Winner of Stage I] allocation. Also, we can incorporate cases enrolled in Stage I as "controls" in the Stage II analysis. The latter is possible because of the Bayesian hierarchical analysis, which leverages information from all subjects in both stages in the analyses.

Probability of an indeterminate result

An indeterminate Stage I result may occur if [BVM-only] cannot be declared superior to [BVM+SGA] and [BVM+SGA] cannot be declared non-inferior to [BVM-only]. Simulations indicate that this scenario is most likely at a treatment effect of ~ 0.5 ICU days. If Stage I yields an indeterminate result after enrolling 3,000 patients, this may suggest that [BVM-only] and [BVM+SGA] do not produce definitively different outcomes for the population studied.

9 Data Management

9.1 Clinical Site Data Management

Each clinical site will maintain study records in locked filing cabinets and/or password protected computers and databases. The site will maintain an essential documents binder, which may be in paper or electronic form.

9.2 Data Coordinating Center

9.2.1 Data Center Description

Overview

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 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.

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 the 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: High availability (HA) – in the event of hardware failure, virtual machines (VM) automatically restart on healthy resources, minimizing impact to end-users; Flexible infrastructure -– compute and storage is seamlessly scaled as current needs change; 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.

9.2.2 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 physically on premise or via a VPN client.

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

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

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

9.3 Electronic Data Capture System

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

10 Study Site Monitoring

The DCC utilizes risk-based monitoring 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 site investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

10.1 Site Monitoring Plan

A supplemental study-specific risk-based monitoring plan will outline 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.

10.2 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.

10.3 Remote Monitoring

The DCC may perform remote monitoring in lieu of on-site monitoring. Remote monitoring involves detailed review of the data entered by the site and consultations with the site investigator and/or research personnel 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.

10.4 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request 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).

11 Protection of Human Subjects

11.1 Risks to Human Subjects

11.1.1 Potential Risks of Patient Participation

Cardiac arrest, trauma and respiratory failure are life-threatening conditions that necessitate immediate airway management intervention. BVM, ETI and SGA are the most widely used prehospital interventions for airway management. Information from preclinical studies support the potential for the study airway interventions to provide a direct benefit to the individual subjects. BVM, ETI and SGA are all standard accepted methods of clinical care for critically ill children. Children enrolled in this study are experiencing a life-threatening event and many will go on to experience severe outcomes, including death. We do not anticipate that participation in the Pedi-PART study will significantly increase or decrease the risk of these outcomes.

Although all of the airway management techniques in this study are commonly used to treat respiratory emergencies, we do not know if one treatment is better than another, or if one of the techniques has greater risks.

Like all medical interventions, some side effects are possible from airway management. Risks of each airway management strategy are summarized in the table below. First pass intubation success is higher for age≥14years. Other risks are not known to vary by age or size.

Method	Bag-Valve Mask Ventilation	Supraglottic Airway Insertion	Endotracheal Intubation
Risks	Inability to ventilate Vomiting leading to regurgitation or aspiration	Inability to Ventilate Airway misplacement Airway dislodgment Injury to airway during insertion Vomiting leading to regurgitation or aspiration	Inability to Ventilate Airway misplacement Airway dislodgment Injury to airway during insertion Vomiting leading to regurgitation or aspiration

There also may be risks that are unknown at this time.

If the assigned strategy of airway management should fail, EMS personnel will administer an alternate method, including advanced airway techniques such as cricothyroidotomy, as is normal practice. Risks associated with the investigation are reasonable in relation to what is known about the medical conditions, and the risks and benefits of available therapies.

Accidental disclosure of protected health information is a risk common to participation in any research study that uses medical records. The study team takes extra measures to ensure protection of confidential information and we never use names of participants when we publish study results.

There are no psychological, social, cultural, financial or legal risks to the patient that are expected with prehospital airway management. There is potential differential risk for adverse events such as hypoxia, aspiration, pneumonitis, and pneumothorax, though equipoise exists and is the premise for establishing these as the primary and secondary outcomes that are being evaluated for this study. This study involves no cost to the pediatric patients or their families.

11.2 Adequacy of Protection Against Risks

11.2.1 Exception from Informed Consent (EFIC)

This study qualifies for ***Exception From Informed Consent (EFIC***) required for emergency research as outlined in FDA regulation 21 CFR 50.24; this section details how the trial addresses each requirement of the regulations.

§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.

Cardiac arrest, trauma and respiratory failure are life-threatening, time-critical conditions that require immediate resuscitation interventions, including immediate airway management interventions. The mortality of pediatric out-of-hospital cardiac arrest is 83–93%.[2, 43, 44] The mortality of pediatric trauma patients undergoing endotracheal intubation is 38.5%.[45] The mortality of pediatric respiratory failure requiring intubation is 56%.[28] There are insufficient scientific data to indicate the best strategy

for prehospital airway management of children with critical illness. There is a paucity of data with sufficient rigor to guide prehospital airway management practices in children. National organizations have singled out the need for rigorous randomized controlled trials comparing prehospital BVM, ETI, and SGA in children to better inform practices.[27]

§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 patients requiring the intervention will be unconscious and unable to provide assent for study enrollment. Parents or legal next-of-kin may be absent; if they are present, there will be insufficient time to obtain informed consent from them as it is essential to begin treatment immediately; they are often in distress when their child is experiencing cardiac arrest, major trauma or respiratory failure. It is not practical for prehospital personnel to explain the study and obtain informed consent (i.e., parental or guardian permission) since they will be focused on providing emergent life-saving interventions for a patient in critical illness. The onset of cardiac arrest, major trauma and respiratory failure are sudden and unpredictable; there is no way to prospectively identify individuals who are likely to become eligible for this trial.

§50.24(a)(3) Participation in research holds out the prospect of direct benefit to the subjects;

Subjects with cardiac arrest, major trauma or respiratory failure are facing a life-threatening situation that necessitates immediate airway management interventions. Preclinical studies and knowledge support the potential for the prehospital airway management interventions to directly benefit these subjects. The risks associated with the investigation are reasonable in relation to what is known about the medical conditions.

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

Cardiac arrest, major trauma and respiratory failure are conditions that occur suddenly and unpredictably. This study could not be conducted without the waiver of consent due to the need to administer the airway management interventions as early as possible after the onset of critical illness.

§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.

Cardiac arrest, major trauma and respiratory failure occur suddenly and require immediate recognition and intervention. Therefore, the available therapeutic window is 0 (zero) minutes. There is inadequate time to identify, locate and communicate with a LAR for a subject within this therapeutic

window.

Although it is highly unlikely to be feasible, the investigators commit to attempting to contact a parent, guardian, legally authorized representative, or adult family member during the therapeutic time window, when feasible, and ask for consent for the subject's participation. If the parent/guardian expresses a desire to discontinue participation, the objection will be noted and research procedures will be discontinued.

If the parent/guardian does not object to continued participation, written notification and age-appropriate assent will be provided at the earliest feasible opportunity. These efforts will be summarized and provided to the IRB at the time of the continuing review.

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

All consent and assent procedures and forms have been approved by the single Institutional Review Board (IRB) of the trial prior to the onset of the trial.

§50.24(a)(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

Prior to trial initiation we will conduct community consultation (CC) activities at each enrolling site. Each site will prepare a community consultation plan, will submit that plan to the IRB for approval, will execute the community consultation, and will provide the results of that consultation to the IRB. The community consultation plans will include opportunities for the community to obtain information about the study, informational materials for distribution, and local input from the community, including from parents or guardians of children in the eligible age range for the study. These strategies will also be used to gather feedback from EMS personnel in these communities.

As part of the community consultation process, the public will also be informed about the options they will have to object to further participation in the trial if an ambulance is called for a pediatric family member with one of the study medical conditions. Each site will have its own individualized consultation plan to meet the needs of its specific community. Large, open public forums will likely not be planned, since the COVID-19 pandemic is still ongoing and community participation in such

events may be unsafe for the public. Furthermore, such forums have had limited success in previous PECARN network studies requiring EFIC.[46–49]

(iii) Public Disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

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 include modalities such as social media or other public service announcements, media coverage such as articles or interviews, posted flyers, information provided via website, and/or presentations to professional organizations and civic groups. Each site will evaluate cultural needs and provide translated materials representative of the affected community and/or the communities from which potential/actual participants are drawn.

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

An independent Data Safety Monitoring Board (DSMB) will exercise oversight of the study as described elsewhere. (Section 12.1)

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

Paralleling procedures enumerated in section (5) for contacting LARs, although it is highly unlikely to be feasible, if there is no LAR available, the investigators commit to attempting to contact an adult family member who is not an LAR during the therapeutic time window, at the earliest feasible opportunity, and ask for consent for the subject's participation. If the family member expresses a desire to discontinue participation, the objection will be noted, and research procedures will be discontinued. If the family member does not object to continued participation, written notification and age-appropriate assent will be provided at the earliest feasible opportunity. These efforts will be summarized and provided to the IRB at the time of the continuing review.

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

subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

Notification of LAR or Other Family

Since this is a study involving only children, research personnel at each site will notify the parent, guardian or LAR of the child about enrollment in the study at the earliest feasible opportunity. This notification will involve a description about the study, including a notification form describing options for continued study participation. Options for ongoing participation may include but not be limited to:

- "I agree to my child's participation in the study, including data collection regarding medical care given for one month following arrival at the hospital or until hospital discharge, whichever occurs last."
- "I object to participation in this study including any further contact or data collection."

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

The majority of children receiving prehospital airway management in each of the participating metropolitan areas are transported to specialty children's hospital Emergency Departments that have research staffing. However, there are numerous other Emergency Departments in each of these metropolitan areas, and most do not have any research personnel; the number of research personnel required to staff all of these Emergency Departments would likely exceed the number of potentially eligible patients who could be enrolled at these other Emergency Departments. Thus, it is not practicable to provide in-person notification in situations when the patient is transported to these non-affiliated Emergency Departments. Therefore, research personnel will make attempts to notify the parent/guardian of these patients by phone and will then notify by mail if phone contact is unsuccessful.

Earliest Feasible Opportunity for Notification

Research personnel will work to ensure that parents, guardians, LARs or other family members of research subjects are notified of study enrollment at the earliest feasible opportunity, typically in the receiving Emergency Department. The earliest feasible opportunity includes consideration of ongoing patient care, the availability of qualified research personnel, the availability of appropriate family members, and the emotional state of available family members. If the earliest feasible opportunity occurs when research personnel are not present in the hospital (typically in the middle of the night or on weekends), clinical staff at affiliated hospitals may provide the parent with written information and a phone number where questions can be answered.

If the patient is transported to a non-affiliated ED where no study-affiliated research personnel are present, study research personnel will make attempts to notify a parent/guardian by phone at the earliest feasible opportunity. If attempts to contact by phone are unsuccessful, research personnel will send appropriate notification forms via mail and/or email. In the event that the research subject is known to have died before notification occurs, research personnel 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.

Opting-Out of the Study

If the adult in attendance with the child at the time of enrollment tells EMS personnel that they object to participation in the trial, EMS personnel will convey that information to research personnel after arrival to the ED as well as the date of the objection. Study-related data collection will be halted from the date/time that EMS personnel received notification of the objection. Once notification of objection is received by the study team, no further data collection or study interventions will be attempted.

At or after the point of study notification, parents/guardians/LARs/family members will be afforded the opportunity to discontinue the subject's participation in the study. At the earliest feasible opportunity to communicate with the patient, research personnel will also give an opportunity for certain minors to object to further participation if they are:

- Determined to be of the age of assent according to local regulations, and
- Have the developmental ability to communicate, and
- Do not have a baseline significant cognitive impairment noted in their medical record that would impair their ability to comprehend information about the trial.

Withdrawn Participants

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

11.2.2 Collection of Mortality and Outcome Data on All Eligible Subjects

Failure to collect outcome and safety data on all patients enrolled in the study would lead to incomplete and potentially biased data collection that would inaccurately assess the effectiveness and safety of the study intervention. Since it is important to ensure that there is no discrepancy in safety outcomes between patients transported to the hospitals where the research team is located and those without research team personnel, it is important to acquire data on mortality for all patients involved in the study. Every effort will be made to obtain medical records for all patients enrolled in the study.

11.2.3 Vulnerable Subjects

Vulnerable populations in this study are children and viable neonates, including Wards of the State. Children will be included because this is a study that focuses on improving outcomes after prehospital pediatric airway management. The focus on children is justified given: 1) the goal of the study is to identify the best approaches to prehospital airway management in critically ill children, 2) children have distinct pathophysiology, anatomy, epidemiology, and methods of clinical care (including airway management) that are much different than for adults. There is no undue concern since care received in the prehospital setting and the emergency department will be administered according to existing patient care protocols/guidelines. Wards of the State are included in the study because there is no way to exclude participants who receive EMS treatment based on custody status.

There is no undue coercion since care received in the prehospital setting will be administered according to existing patient care protocols/guidelines. Research in children involves special protections under 45 CFR §46 Subpart D "Additional DHHS protections for children involved as subjects in research" and 21 CFR §50 and §56. The study in this protocol is permissible under these regulations as:

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

Wards of the State enrolled in this study do not qualify for the waiver of documentation as per federal regulations (subpart D). A signature from the legal guardian will be required in order to use any data collected. Subjects identified as a ward of the state will receive notification similarly to any other subject enrolled in the study. However, it is unlikely that the person who is initially notified of the enrollment will be a legal guardian (e.g. foster parent or temporary guardian). The decision of the person who is first notified of the enrollment will be followed until the legal guardian is reached. Every effort will be made to locate and obtain a signature from the legal guardian of the enrolled child in order to obtain permission to use any data that is collected. Sites will be required to complete a note-to-file outlining notification efforts and the relationship of the legal guardian who is approached for signature. Additionally, sites will work with their local IRBs, as required, to meet any local regulations regarding enrollment of wards of the state, should they be more restrictive than the regulations outlined in the protocol and approved by the SIRB.

11.2.4 Institutional Review Board and Human Research Protection

The Institutional Review Board (IRB) at the University of Utah will serve as the single IRB (sIRB). The Utah IRB has extensive experience with single IRB implementation, including 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.

11.2.5 Protections Against Risk

Because the study methods of airway management are current standard of care, the intervention itself does not pose an additional risk to enrolled subjects. If the assigned method of airway management should fail for some reason, EMS personnel will administer an alternative method, as is normal practice.

Expertise of Providers

Children eligible for this study are cared for by expert prehospital personnel with training in pediatric airway management and are transported to emergency departments that are staffed by qualified physicians and nurses. Subjects are evaluated continuously in the emergency setting, and receiving centers are well prepared to evaluate and treat any complications that can arise from participation in the study.

Loss of Confidentiality

The minimal risk of loss of privacy is mitigated by the substantial data management resource and security described in Section 9.2.2.

11.3 Potential Benefits of Proposed Research

Participants have the potential for direct benefit because some airway management techniques may be easier and faster to use or help provide oxygen to the body with fewer complications. What we learn from this study may help children in the future who experience a life-threatening breathing emergency and may help EMS agencies develop protocols to provide better care for children.

11.4 Importance of the Knowledge to be Gained

Children with critical illness face a life-threatening situation that necessitates immediate intervention. Information from preclinical studies support the potential for the study airway interventions to provide a direct benefit to the individual subjects. For example, if SGA were to prove non-inferior to BVM, this would support the use of primary SGA in the care of critically ill children, lessening the burden of airway training and skills maintenance. If BVM were to prove superior to SGA, this would affirm current practice as the optimal approach, prompting the need for initiatives to improve or expand EMS personnel training.

The risks to subjects are minimal relative to the importance of the knowledge to be gained. All three airway techniques are widely used in current prehospital clinical practice. The findings from this trial will aid individuals directly and society more generally by indicating the best resuscitation techniques that should be used by EMS personnel, allowing EMS system to focus training resource upon effective measures.

12 Data and Safety Monitoring Plan

12.1 Data Safety Monitoring Board (DSMB)

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

12.2 Adverse Event Reporting

For purposes of this study, adverse events are detected 30 minutes after Emergency Department arrival through hospital discharge or 72 hours after ED arrival, whichever occurs first. The first 30 minutes of Emergency Department arrival will be used to establish baseline conditions. Events that occur prior to the first 30 minutes of the Emergency Department arrival will not be reported as adverse events; these should be recorded as baseline conditions and monitored for frequency as a part of the routine safety analysis (e.g., in DSMB reports). Events that occur in the first 30 minutes, and expected adverse events such as those listed in Table 2 will not be reported as separate SAEs but will be collected as data elements and will be monitored by the medical monitor and DSMB. However, if the event is serious, unexpected, and possibly/probably/defiantly related then it will still be reported as an SAE. Events that occur following discharge from the hospital or 72 hours after ED arrival will not be reported as adverse events.

12.2.1 Definition of Adverse Event and Serious Adverse Event

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

Serious Adverse Event (SAE)
The FDA defines a serious adverse event (SAE) as 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.

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

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

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 and may **not** be assessed by a research coordinator.*

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

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

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

Definitely Related The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention and it is clear that the event was caused by study participation. An alternate cause is unlikely.

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.

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 subject's clinical state immediately prior to the event. Examples of some expected events for this study are listed in table 2: Safety Endpoints.

Not Expected An event is considered not expected 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:

- 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/Fatal
- Not Recovered or Not Resolved
- Recovered or Resolved (returned to baseline)
- Recovered or Resolved with Sequelae
- Recovering or Resolving
- Unknown

12.2.3 Data Collection Procedures for Adverse Events

Other adverse events (including serious adverse events) identified in the AE monitoring window will be recorded and evaluated for relatedness, severity, and expectedness.

AE identification will be through medical record review of the prehospital and hospital records. The site investigator will determine the AE status as well as seriousness, relatedness, and expectedness, as appropriate. 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. If an AE is serious, unexpected, and related, it will be reported to applicable regulatory agencies according to IRB, FDA, and NIH reporting policies, generally within 7 days of initial receipt of information.

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

12.2.4 Unanticipated Problems (UP)

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related or possibly to participation in the study, and suggest that research places subjects at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event. The medical monitor for the study will assess the report. Any unanticipated problems involving risks to human subjects will be reported to the University of Utah IRB within 14 days of DCC receipt of the investigator report.

12.2.5 Trial Stopping rules

In the unlikely event that the medical monitor believes an unexpected and study-related SAE or an unanticipated problem warrants emergent cessation of enrollment in the trial, NHLBI staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the NHLBI staff and the DSMB chairperson cannot be reached expeditiously, the Data Coordinating Center will notify the study investigator (Dr. Wang) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB. The sIRB in Utah will be notified, and each site investigator will notify their institutional Human Research Protection program of the trial suspension. After notification of the NHLBI Program Official or Project Officer, and the DSMB chairperson, of serious, unexpected, and study-related adverse events or unanticipated problems (UP) that warrant emergent suspension of enrollment, decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Wang) and all clinical investigators, who will be instructed to report this to their institutional Human Research Protection program.

12.2.6 Monitoring Serious Adverse Events

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

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

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

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

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

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

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

12.4 Reporting to the Food and Drug Administration

Serious, unexpected and related adverse events will be reported to the FDA in an expedited manner consistent with FDA requirements. The Data Coordinating Center will prepare the report for submission by the principal investigator, Dr. Wang, who will hold the IDE.

13 Study Training

13.1 Study Training

A formal training program for investigators and research personnel 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 Exception from Informed Consent process. No site will be activated until all training requirements have been fulfilled by the site investigators and research personnel.

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

All EMS personnel who perform study interventions in the participating EMS agencies will be informed about the details of the study before any patient enrollment begins so that they are aware of the study and know how to notify research personnel at the hospital if an adult family member of the patient informs them of their desire not to have the patient's data utilized for the study. The number of trainings in each EMS system will be determined based on EMS system logistics to ensure that all providers can obtain the training at least once.

14 Regulatory Considerations

14.1 Food and Drug Administration

This study is being conducted under Exception from Informed Consent (EFIC). For that reason, Investigational Device Exemption (IDE) G230073 has been filed to cover the airway management strategies.

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

14.2 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth, the date of the episode, hospital admission, hospital discharge, readmissions within 30 days, and death. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events.

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

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

14.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on sex, race, or ethnicity, except women who are known or visibly pregnant

14.4 ClinicalTrials.gov Requirements

The Pedi-PART trial will be registered at https://clinicaltrials.gov in accordance with Federal regulations.

14.5 Retention of Records

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

14.6 Public Use Data Set

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

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

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

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