Title:	**OPTImal Ventilation to Improve Pediatric Cardiac Arrest Outcomes (OPTI-VENT)**
Short Title	Optimal Ventilation for Cardiac Arrest
Regulatory Sponsor:	
eIRB Number	IRB 24-022623
Protocol Date:	October 11, 2024

Amendment 1 Date: September 29, 2025 Amendment 3 Date: January 20, 2026

Amendment 2 Date: November 14, 2025 Amendment 4 Date:

Sponsor: NIH/NICHD

Study Principal Investigator: Robert Michael Sutton MD MSCE
9th Floor Main Building: Room 9NW66
3401 Civic Center Blvd., Philadelphia, PA, 19104
Phone 267-273-3919
email: suttonr@chop.edu

Site Principal Investigators:

Ryan W. Morgan MD MTR and Amanda O'Halloran MD

The Children's Hospital of Philadelphia

9th Floor: Main Building CCM Suite
3401 Civic Center Blvd., Philadelphia, PA, 19104
email: morganr1@chop.edu and ohallorana@chop.edu

TABLE OF CONTENTS

Table of Contents ..... *ii*

Abbreviations and Definitions of Terms ..... *iv*

Abstract ..... *v*

Protocol Synopsis ..... *vi*

1 Background Information and Rationale *1*

1.1 Introduction **1**

1.2 Name and Description of Investigational Product or Intervention **1**

1.3 Findings from Non-Clinical and Clinical Studies **1**

1.4 Relevant Literature and Data **2**

1.5 Compliance Statement **2**

2 Study Objectives *2*

2.1 Primary Objective (or Aim) **3**

3 Investigational plan *3*

3.1 General Schema of Study Design **3**

3.1.1 Screening Phase 3

3.2 Allocation to Treatment Groups and Blinding **3**

3.3 Study Duration, Enrollment and Number of Sites **4**

3.3.1 Duration of Subject Study Participation 4

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected 4

3.4 Study Population **4**

3.4.1 Subject Inclusion Criteria 4

3.4.2 Subject Exclusion Criteria 4

4 Study Procedures *5*

5 Study Evaluations and Measurements *6*

5.1 Screening and Monitoring Evaluations and Measurements **6**

5.1.1 Medical Record Review 6

5.2 Efficacy Evaluations **6**

5.2.1 Diagnostic Tests, Scales, Measures, etc. 6

6 STATISTICAL CONSIDERATIONS *7*

6.1 Primary Endpoint **7**

6.2 Secondary Endpoints **8**

6.3 Statistical Methods **8**

6.4 Sample Size and Power **9**

6.5 Interim Analysis **10**

7 Study INTERVENTION 11
7.1 Description 11
8 SAFETY MANAGEMENT 12
8.1 Clinical Adverse Events 12
8.2 Adverse Event Reporting 12
9 STUDY ADMINISTRATION 12
9.1 Treatment Assignment Methods 12
9.1.1 Randomization 12
9.2 Data Collection and Management 12
9.3 Confidentiality 13
9.4 Regulatory and Ethical Considerations 14
9.4.1 Data and Safety Monitoring Plan 14
9.4.2 Risk Assessment 14
9.4.3 Potential Benefits of Trial Participation 15
9.4.4 Risk-Benefit Assessment 15
9.5 Recruitment Strategy 15
9.6 Informed Consent/Assent and HIPAA Authorization 15
9.6.1 Main Study 15
9.6.2 Waiver of Consent 15
10 PUBLICATION / Dissemination 16
11 References 16

ABBREVIATIONS AND DEFINITIONS OF TERMS

AHA	American Heart Association
BPM	Breaths per minute
CC	Chest Compression
CPR	Cardiopulmonary resuscitation
IHCA	In-hospital cardiac arrest
ICU	Intensive care unit
PCPC	Pediatric Cerebral Performance Category
pediRES-Q	Pediatric Resuscitation Quality of CPR Collaborative A multicenter pediatric cardiac arrest resuscitation quality collaborative collecting standard cardiac arrest data across >50 domestic/international sites.

ABSTRACT

Context:

In 2020, the American Heart Association (AHA) increased the recommended cardiopulmonary resuscitation (CPR) ventilation rate from 10 breaths per minute (bpm) to a range of 20 – 30 bpm. Unfortunately, providers do not achieve this recommended target in actual practice. In response, we developed an OPTImizing VENTilation (*OPTI-VENT*) QI bundle consisting of provider education and point-of-care CPR ventilation rate guidance (CPR cue cards and a ventilation rate metronome) that demonstrated efficacy to train providers to a specific ventilation rate with high compliance in a single-center investigation.

Objectives:

Our primary objective is to evaluate the effectiveness of the *OPTI-VENT* bundle to improve survival to discharge with favorable neurological outcome among children receiving at least 1 minute of intensive care unit (ICU) CPR.

Study Design:

Parallel-stepped-wedge hybrid cluster-randomized trial

Setting/Participants:

Across 20 domestic academic children's hospitals, children ≥37 weeks corrected gestational age and <18 years old with an invasive airway in place at the time of an ICU cardiac arrest or who had an airway placed during the first 5 minutes of CPR are eligible for inclusion.

Study Interventions and Measures:

Standard cardiac arrest data collection will be completed for cardiac arrest subjects from the electronic medical record, continuous bedside monitors, and other patient physiologic monitoring devices (e.g., near infrared spectroscopy [NIRS]) for pre-, intra-. and post-arrest time periods.

The primary outcome is survival to hospital discharge with favorable neurologic outcome, defined as a Pediatric Cerebral Performance Category score of 1-2 or no change from baseline. Secondary outcomes will be survival to discharge, return of spontaneous circulation (ROSC) >20 minutes, return of circulation (ROC) with extracorporeal support, substantive new morbidity among survivors (increase in Functional Status Scale score ≥3), intra-arrest cerebral oxygen saturation, and proportion of events 1) that achieve diastolic blood pressure (DBP) thresholds during CPR, and 2) with either hyperoxia or hypocarbia in the immediate post-arrest period.

PROTOCOL SYNOPSIS

Study Title	OPTImal Ventilation to Improve Cardiac Arrest Outcomes
Funder	National Institute of Child Health and Human Development
Clinical Phase	NA
Study Rationale	In 2020, the American Heart Association (AHA) increased the recommended CPR ventilation rate from 10 breaths per minute (bpm) to a range of 20 – 30 bpm, a target associated with better outcomes. Unfortunately, providers do not achieve this recommended target in actual practice. As such, innovative training strategies to this CPR parameter are potential therapeutic interventions to rescue more children from cardiac arrest. To that end, we developed an OPTImizing VENTilation (*OPTI-VENT*) bundle consisting of provider education and point-of-care CPR ventilation rate guidance (CPR cue cards and a ventilation rate metronome). Our bundle demonstrated efficacy to train providers to a specific ventilation rate with high compliance. In this protocol, we describe an adaptive, parallel-stepped-wedge hybrid cluster-randomized trial to determine if the *OPTI-VENT* bundle can improve cardiac arrest outcomes by training providers to the 2020 CPR ventilation rate.
Study Objective(s)	**Primary** • To evaluate the effectiveness of the *OPTI-VENT* bundle to improve survival to discharge with favorable neurological outcome (Pediatric Cerebral Performance Category Score 1-2 or no change from baseline) among children receiving at least 1 minute of CPR. **Secondary** • Evaluate the effectiveness of the OPTI-VENT bundle to achieve AHA ventilation targets. **Analytic Observational Objectives** • Determine if there is an alternative ventilation rate that is associated with improved 1) survival outcomes and 2) intra-arrest physiology (e.g., blood pressure). • Determine the association between Airway Opening Index (a newly discovered ventilation metric) and 1) survival outcomes, and 2) intra-arrest physiology (e.g., blood pressure and exhaled carbon dioxide) • Determine if AOI can be modified by changing airway pressures delivered during CPR using novel multidimensional machine learning algorithms.
Test Article(s) *(If Applicable)*	**OPTI-VENT QI Bundle Description:** **Provider Education:** There are two main components to the provider education: 1) low-intensity / high-frequency point-of-care training and 2) monthly integration into existing education or quality meetings. Point-of-care training will be conducted by pediRES-Q network site quality physician champions. During this brief (<2 minute) bedside education, the educator will 1) review the AHA CPR ventilation rate target, and 2) ensure the provider has their rate cue card on his/her person and knows how to activate the CPR ventilation rate metronome described below.

	Additionally, a focus on CPR ventilation rates will be integrated into resuscitation education or quality meetings for all disciplines. A brief Microsoft PowerPoint presentation focusing on the benefits of ventilation rate compliance will be standardized for distribution across all sites. "Report cards" detailing unit-level performance will be generated by the University of Utah Data Coordinating Center and emailed to the PIs for review during their monthly presentations. **Point-of-Care Guidance:** Similar to the single-center study supporting our multicenter trial, we will deploy a metronome to all cardiac arrests. In the single-center *OPTI-VENT* study, a smart phone application was used. For this multicenter trial, we will use a similar method or leverage the existing pediRES-Q infrastructure which already deploys CPR feedback defibrillators to all cardiac arrest events.
Study Design	Prospective hybrid cluster randomized stepped-wedge interventional multicenter trial
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Children ≥37 weeks corrected gestational age and <18 years of age 2. Invasive airway in place at the start of CPR or airway placed within the first 5 minutes 3. Received at least 1 minute of CPR. **Exclusion Criteria** 1. Lack of commitment to aggressive ICU therapies (e.g., CPR performed as part of end-of-life care. 2. Brain death determination prior to the CPR event. 3. Out-of-hospital cardiac arrest was the reason for initial admission to the hospital (known poor outcomes). 4. Supported by Veno-Arterial Extra Corporeal Membrane Oxygentation at the start of CPR Healthcare providers inclusion criteria: bedside care providers of all disciplines working in ICU Healthcare provider exclusion criteria: none
Number Of Subjects	Total Number of Subjects: 1530 Total Number at CHOP: 200 (estimated) Total Number of Sites: 20
Study Duration	Each subject's participation will last from the time of their cardiac arrest (CPR event) to their discharge from the hospital or death. Subjects alive 30 days after the end of the 4.25-year enrollment period will have their final outcome data assessed at that time.
Study Phases	Cardiac arrest data (e.g., subject demographics, intra- and peri-arrest physiologic waveforms, outcome data) will be collected on all subjects meeting inclusion / exclusion criteria. There is no identifying information collected on the ICU care providers who work in the participating ICUs.

Recruitment and Informed Consent: Cardiac Arrest Subject: As this study is observational at the patient level, similar to other pediRES-Q network quality improvement interventional studies, a waiver of consent will be requested. This is also exactly similar to the consent process utilized for Dr. Sutton's now published *ICU-RESUS* interventional trial (*Journal of the American Medical Association*) which implemented a similar training bundle to ICU providers, albeit focused on the chest compression aspect of CPR rather than ventilation. A waiver will be requested on the following factors: 1) This study poses no more than minimal risk (CPR training already exists at the participating hospitals and quality will be at least as good with *OPTI-VENT* implementation); 2) The waiver will not adversely affect the rights and welfare of the subjects (i.e., cardiac arrest patients undergoing CPR); 3) Obtaining informed consent would threaten the scientific validity of the study. The scientific validity of the study is dependent upon capturing all eligible events during the period of study, as one of the major goals is to associate ventilation data with survival outcomes; 4) This study involves no therapeutic intervention at the patient level (no drug, no technology), and there are no changes in accepted clinical practice; 5) Only a limited dataset will be shared with the University of Utah and Villanova University. The minimal risk of loss of privacy will be mitigated by the substantial data management resources of the data management team at CHOP and the process by which they verify that only a limited dataset is sent to the University of Utah and Villanova University for analysis. As presently accepted in other pediRES-Q protocols, waiver of HIPAA authorization at the patient level will also be requested, as again, no identifying information will be transmitted outside of CHOP. Healthcare Provider: 1) This study poses no more than minimal risk (CPR training already exists in ICUs and is a normal job-related responsibility and there are no links between the providers identify and their performance, either in the educational session or during actual patient care); 2) The research cannot be practically carried out without the waiver as it will be important to describe how the participating sites implemented the bundle. Additionally, consenting all providers would place undue burden on these healthcare providers who are caring for critically ill children who by definition have labor intensive care plan; 3) There are also no identifying links between the care providers and their resuscitation performance; 4) The waiver will not adversely affect the rights and welfare of the subjects as CPR training already exists in ICUs and is a normal job-related responsibility. The minimal risk of loss of privacy will be mitigated by the substantial data management resources of the data management team at CHOP and the process by which they verify that only a limited dataset is sent to the University of Utah and Villanova University for analysis. As presently accepted in other pediRES-Q protocols, waiver of HIPAA

	authorization at the patient level will also be requested, as again, no identifying information will be transmitted outside of CHOP.
Efficacy Evaluations	The primary outcome is survival to hospital discharge with favorable neurologic outcome, defined as a PCPC score of 1-2 or no change from baseline.
Pharmacokinetic Evaluations	NA
Safety Evaluations	NA
Statistical And Analytic Plan	The analysis of survival to discharge with favorable neurological outcome is based on all enrolled *index* events excluding transition periods. For the primary analysis, a mixed effect logistic regression model will be fit with our primary outcome as the dependent variable. The primary predictor will be treatment group, an indicator of whether the *OPTI-VENT* bundle was fully implemented prior to the arrest. Fixed covariates will be illness category (e.g., medical cardiac, medical non-cardiac, surgical cardiac), age, first documented rhythm, and time since trial start (to prevent confounding due to unrelated temporal changes in outcome), and time of day (weekday versus night or weekend). Etiology and severity of pre-existing lung disease will be evaluated as a confounder / effect modifier. Unit will be included as a random effect to account for heterogeneity in patient outcomes across ICUs and to accommodate clustering of patients within ICUs. The null hypothesis will be tested using the standard type III test for the fixed effect, and the p-value for the two-sided alternative will be presented.
DATA AND SAFETY MONITORING PLAN	Despite CPR training existing in ICUs as a job-related responsibility and this investigation being observational at the subject-level, as we did for the *ICU-RESUS* trial, we plan to assemble a DSMB in collaboration with the *Eunice Kennedy Schriver* National Institute of Child Health and Human Development (NICHD) for this study. The DSMB is responsible for monitoring subject safety, accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual clinical centers, and review of formal interim statistical analyses of treatment efficacy. DSMB meetings will be scheduled as follows: full DSMB meeting after 1, 2, 3, and 4.5 years of enrollment; chair only review at, 1.5, 2.5, and 3.5 years. Efficacy will be formally assessed at 2, 3, and 4.25 years. A symmetric, two-sided O'Brien-Fleming type boundary with overall alpha level set to 0.05 will be used as a guideline for stopping the study due to a difference between treatment arms. Stopping boundaries will be generated using symmetric monitoring boundaries, corresponding to alpha spending of 0.025 to detect a benefit and 0.025 to detect a harmful effect of treatment vs control. Lan-DeMets spending functions corresponding to O'Brien-Fleming type boundaries will be used. Monitoring boundaries will be set according to the proportion of total statistical information (information fraction) available in each interim analysis dataset Futility analyses will not be performed for

	this minimal risk study because futility for the primary endpoint does not diminish the value of fully enrolling for other objectives.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Pediatric cardiac arrest is a life-threatening problem affecting >15,000 hospitalized children each year (1). Less than half of these children survive to hospital discharge, and neurologic morbidity is common among survivors. Moreover, pediatric cardiac arrest survival outcomes plateaued nearly ten years ago, highlighting the critical need for evidence-based and innovative therapeutic approaches (2).

Our team has established that high-quality cardiopulmonary resuscitation (CPR) improves outcomes from pediatric cardiac arrest (3). To date, an imbalance exists with overwhelmingly more investigation into chest compression (CC) quality (i.e., depth, rate, and release velocity) as compared to the delivery of ventilations. Given that most pediatric patients have respiratory disease at the onset of cardiac arrest (4), the lack of rigorous investigation into optimal CPR ventilation strategies represents a significant roadblock to understanding how best to rescue more children from cardiac arrest.

1.2 Name and Description of Investigational Product or Intervention

The *OPTI-VENT* bundle consists of two main components: 1) provider education: physician, registered nurse, and respiratory therapist education (via scheduled existing educational or quality meetings) and 2) point-of-care ventilation guidance (CPR cue cards highlighting ventilation rate targets and the introduction of a ventilation rate metronome). The primary ventilation training targets will be: 30 breaths per minute (bpm) for infants < 1 year of age (1 breath every 2 seconds) and 20 bpm for older children (1 breath every 3 seconds), consistent with 2020 AHA Guidelines (5) .

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1.1 Clinical Studies in Children

- In a previous NHLBI-funded multicenter study (6), we evaluated the association between CPR ventilation rates and survival. In this study of 47 intubated children who suffered a cardiac arrest, "high ventilation rates," defined as ≥30 bpm among infants <1 year of age and ≥25 bpm among older children, were associated with a more than 4x greater likelihood of survival to hospital discharge with favorable neurologic outcome (primary outcome of this investigation). Our data were translated by the AHA CPR Guideline committee into a target rate of 20 – 30 bpm.
- The *OPTI-VENT* bundle provider education in our pilot work followed a "low-intensity / high frequency" (spaced learning) training paradigm. Our team has pioneered this approach (7), documenting its effectiveness to improve compression quality. In a single-center study, the *OPTI-VENT* bundle improved ventilation rate target compliance (absolute risk reduction of ventilation rates exceeding 30 bpm: 22%, [CI95 16% – 28%], p<0.001) (8).
- A recent landmark study established that intrathoracic airway closure impacts CPR ventilation (9). In this 3-part series of investigations, end-tidal carbon dioxide ($ETCO_2$) waveforms – waveforms that are part of standard clinical care in ventilated patients in ICUs – were used to infer the degree of airway closure during CPR. Importantly, the degree of airway closure could be mitigated, and the ventilation during CPR improved, by small increases in the amount of airway pressure delivered during CPR. By maintaining airway patency, the chest compression oscillations provide a tidal volume (i.e., size of the delivered breath) that is additive to the tidal volume provided by the rescuer during CPR.

1.4 Relevant Literature and Data

Background: Of the >15,000 US children who have a pediatric in-hospital cardiac arrest (p-IHCA) each year, only ~40% survive (1). Interventions to improve CPR quality can save lives, but to date, there is a research imbalance, with much more of a focus on optimal chest compression techniques as compared to ventilation strategies. Using data extrapolated from adult studies, previous iterations of CPR Guidelines recommended a ventilation rate of 10 bpm for both children and adults. This recommendation was based upon the concern that higher ventilation rates would detrimentally affect hemodynamics during pediatric CPR as well (i.e., decreased venous return from increased intrathoracic pressure)(10, 11). In contrast, our NIH-funded multicenter observational data found that higher ventilation rates were beneficial to children (6). As a result, in 2020, the AHA increased the CPR ventilation rate from 10 bpm to 20 – 30 bpm. Due to the small number of patients and observational nature of our preliminary work, there remains intense controversy across the seven international resuscitation councils (e.g., AHA, European Resuscitation Council [ERC]) regarding optimal pediatric CPR ventilation rates. While the AHA recommends 20 – 30 bpm, the ERC recommends a range of 10 – 25 bpm (25 bpm for infants down to 10 bpm for anyone over 12 years). All councils classify their pediatric ventilation rate recommendation as "weak," with "very low level of evidence," and list ventilation rate as a research gap that requires high priority multicenter evidence to inform future guidelines.

Resuscitation Care Bundles (*ICU-RESUS*): We recently published findings from a large (>1000 patients) NHLBI-funded multicenter trial evaluating physiologic-directed point-of-care CPR education and cardiac arrest reviews with a focus on improving chest compression quality (NCT02837497) in the *Journal of the American Medical Associatio*n (12). In contrast to the ventilation-targeted intervention we propose in this investigation, the *ICU-RESUS* bundle focused specifically on the chest compression aspect of CPR with the goal to improve intra-arrest diastolic blood pressure (DBP). And while the *ICU-RESUS* trial demonstrated our ability to implement a bundled intervention across a diverse group of ICUs with high compliance (>90%), we did not observe an improvement in patient outcomes with implementation of the chest compression targeted intervention. Given the high incidence of respiratory disease at the onset of cardiac arrest in children, we suspect that not including ventilation rate-focused training (CPR ventilation rate compliance was <6% among *ICU-RESUS* subjects) was a key driver of *ICU-RESUS* bundle "failure," and thus, made the *OPTI-VENT* trial the next logical step.

1.5 Compliance Statement

The investigators will perform the study in accordance with this protocol and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study. All episodes of noncompliance will be documented.

2 STUDY OBJECTIVES

In an adaptive, parallel-stepped-wedge hybrid cluster-randomized trial, the purpose of the study is to determine if the *OPTI-VENT* bundle can improve pediatric cardiac arrest outcomes by training providers to the 2020 CPR ventilation rate (20-30 bpm).

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine the effectiveness of the *OPTI-VENT* bundle to improve survival to discharge with favorable neurological outcome among children receiving at least 1 minute of CPR.

In embedded observational studies, the secondary objectives are to:

- Determine if there is an alternative ventilation rate that is associated with improved 1) survival outcomes and 2) intra-arrest physiology (e.g., blood pressure).
- Determine the association between Airway Opening Index and 1) survival outcomes and 2) intra-arrest physiology (e.g., blood pressure and exhaled carbon dioxide)
- Determine if AOI can be modified by changing airway pressures delivered during CPR using novel multidimensional machine learning algorithms.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This study is a prospective hybrid cluster randomized stepped-wedge interventional multicenter trial to evaluate the effectiveness of an educational QI bundle focused on CPR ventilation rate to improve survival outcomes when providers are trained to existing American Heart Association (AHA) Guidelines (20 – 30 breaths per minute [bpm]). It is essentially a platform trial, leveraging the existing infrastructure and database of the pediRES-Q network.

3.1.1 Screening Phase

Potential subjects will be screened from all cardiac arrest subjects at participating study sites using this protocol's inclusion and exclusion criteria. All subjects ≥37 weeks corrected gestational age and <18 years old with an invasive airway in place at the time of a cardiac arrest or who had an airway placed during the first 5 minutes of CPR, and who required at least 1 minute of CPR will be enrolled.

Providers who work in the ICU are also potential subjects of this investigation. No identifying information will be collected that could be used to provide a link to their actual CPR performance.

3.2 Allocation to Treatment Groups and Blinding

The basis of this investigation is a hybrid between a parallel and stepped-wedge cluster-randomized trial (13). As in a parallel design, 4 randomly selected sites will be permanently assigned to enroll in the control group, and 4 others will be permanently assigned to enroll in the intervention group. The remaining 12 sites, as in a stepped-wedge design, will initially enroll in the control group but will be randomly assigned a time to begin implementing the intervention. Data collection will be continuous for the entire 4.25-year study, but events enrolled in the 8-week transition period after the intervention is initiated will be excluded from analyses comparing intervention to control. In order to ensure roughly equal numbers of subjects in the intervention and control groups, and to ensure balance with respect to baseline pre-trial survival rates, the computer-generated randomization schedule will be selected from all possible configurations with sufficient expected balance in both expected enrollment and pre-trial survival rates.

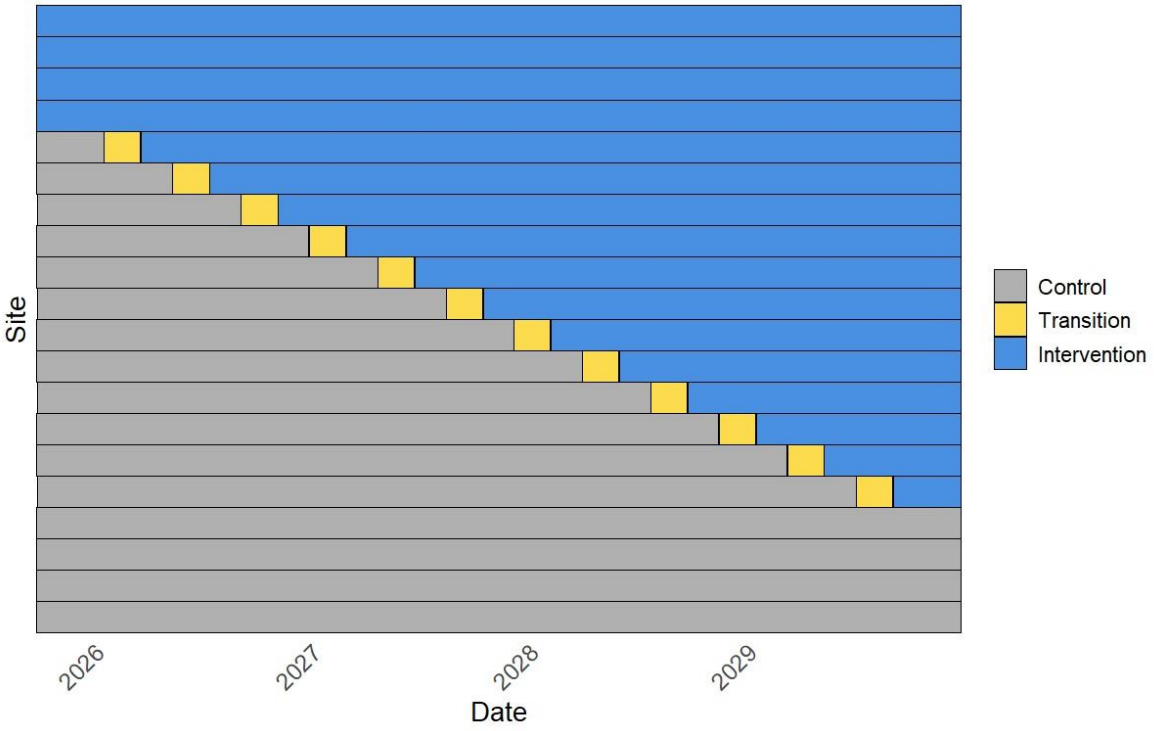


Figure 1: Schematic summary of overall study design

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Subject Study Participation

The study duration per subject will be from the time of their cardiac arrest through hospital discharge or death. Subjects alive 30 days after the end of the 4.25 year enrollment period will have their final outcome data assessed at that time.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at approximately 20 investigative sites in the United States.

Recruitment will stop when approximately 1530 subjects are enrolled. As per the study design, enrollment will end 4.25 years from study start.

3.4 Study Population

3.4.1 Subject Inclusion Criteria

All children ≥37 weeks corrected gestational age and <18 years old with an invasive airway in place at the time of a cardiac arrest or who had an airway placed during the first 5 minutes of CPR, and who required at least 1 minute of CPR.

3.4.2 Subject Exclusion Criteria

1) Lack of commitment to aggressive ICU therapies (e.g., CPR performed as part of end-of -life care as documented in the medical record)
2) Brain death determination prior to the CPR event

3) The admission to the hospital was secondary to an out-of-hospital CPR event (known poor outcomes if there is a recurrent arrest)
4) Supported by Veno-Arterial ECMO at the start of CPR

Healthcare provider inclusion criteria: bedside care providers of all disciplines working in ICU

Exclusion criteria: none

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

Standard cardiac arrest data (e.g., demographics, intra- and post-arrest physiologic variables, CPR quality variables) will be collected on all subjects, extracted from the electronic medical record, continuous bedside monitors, and other patient physiologic monitoring devices (e.g., NIRS). Data elements to be collected from the pre-, intra-, and post-arrest periods include but are not limited to:

Patient Characteristics: date of birth; sex; race/ethnicity; height; weight; illness category (medical cardiac, medical non-cardiac, surgical cardiac, surgical non-cardiac, trauma). Pre-existing conditions: respiratory insufficiency; hypotension; congestive heart failure; pneumonia; sepsis; trauma; renal insufficiency; malignancy; congenital heart disease, if yes, single ventricle; if single ventricle, the anatomy is specified; if surgical palliation completed, type of most recent surgical procedure is noted (Norwood with Sano modification, Norwood with modified BT shunt, Hybrid Procedure, Bi-directional Glenn, Fontan, other); vasoactive inotropic scores (2 hours preceding CPR); pediatric cerebral performance category (PCPC) score; functional status scale (FSS) score.

CPR Event Characteristics: interventions at CPR start (e.g., vasoactive infusion); immediate cause of arrest (Y/N for hypotension, respiratory decompensation, arrhythmia, cyanosis without respiratory decompensation); first documented rhythm requiring CPR; time of first shockable rhythm; pre-shock pause (seconds); time of first defibrillation; time of first vasopressor administration for non-shockable rhythm; drug interventions during CPR; duration of CPR (minutes). CPR mechanics variables: Compression depth (mm); rate (per minute); chest compression fraction; and leaning during relaxation phase (release velocity, if available [mm/second]). Ventilation variables: $ETCO_2$ (mmHg); ventilation rate (bpm); airway opening index; other ventilation variables as available (e.g., Peak Inspiratory Pressure [cmH_2O]). Intra-arrest physiology (arterial BP (mmHg), $ETCO_2$ (mmHg), and arterial/venous blood gases.

Post-cardiac Arrest Care Variables (first 6 and >6-24 hours post-arrest with highest and lowest unless indicated): systolic and diastolic arterial BP (mmHg); temperature (°C); arterial PaO2 (mmHg); PaCO2 (mmHg); pH; highest lactate (mmol/L); glucose (mg/dL); vasoactive scores (6, 12 and 24 hours); required extracorporeal membrane oxygenation (ECMO) support (Y/N); targeted temperature management (TTM, Y/N); if TTM, goal max temperature; electroencephalography (EEG; Y/N).

ICU Care Providers: No identifying information will be collected from the providers working in the ICUs who may be targeted with the training intervention. During bedside trainings described below, only shift (AM [7am to 7pm], PM [7pm to 7am]), discipline (MD, RN, RT, other) and time since last training (<1 week, <1 month, >3 months) will be recorded. These variables are used to be able to describe the spread of the *OPTI-VENT* training.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

All data elements to be collected are entered into the electronic medical record as part of routine clinical care.

5.2 Cardiac Arrest Event Data:

Data recorded during the chest compression event include but are not limited to those listed in Section 4.

5.3 Patient Characteristics

Patient characteristics to be collected include but are not limited to those listed in Section 4. The only PHI data collected will be subject name, MRN, date of birth, and date of the event, which will be kept confidential in accordance with Institutional policies and HIPAA IRB regulations. The only PHI that will be entered into REDCap database will be date of birth and date of arrest.

5.4 Post-Resuscitation Phase

Data elements to be collected include but are not limited to those outlined in Section 4.

5.5 Efficacy Evaluations

The primary outcome is survival to hospital discharge with favorable neurologic outcome, defined as a PCPC score of 1-2 or no change from baseline.

Secondary outcomes will be:

- survival to discharge
- Return of spontaneous circulation (ROSC) >20 minutes
- Return of circulation with ECMO support
- Substantive new morbidity among survivors (increase in Functional Status Scale score ≥3)
- Intra-arrest cerebral oxygen saturation (%) as measured by Near Infrared Spectroscopy (NIRS) monitors, as part of standard clinical care in the pedRES-Q sites.
- Proportion of events 1) that achieve the DBP recommended thresholds during CPR (14), and 2) with either hyperoxia (PaO2 >300 mmHg) or hypocarbia (PaCO2 <30 mmHg) in the immediate post-arrest period (15).

5.5.1 Diagnostic Tests, Scales, Measures, etc.

Table 1: Pediatric Cerebral Performance Category (from medical record review)(16)

Score	Category	Description
1	Normal	Age-appropriate level of functioning In preschool-aged children, appropriate development In school-aged children, attendance in regular classes
2	Mild disability	Can interact at an age-appropriate level Minor neurologic disease that is controlled and does not interfere with daily functioning (eg, seizure disorder) In preschool-aged children, possibly minor developmental delays, but with > 75% of all daily living developmental milestones above the 10th percentile In school-aged children, attendance in regular school but in a grade that is not appropriate for age or in the appropriate grade but failing because of cognitive difficulties
3	Moderate disability	Below age-appropriate functioning Neurologic disease that is not controlled and severely limits activities In preschool-aged children, most daily living developmental milestones below the 10th percentile In school-aged children, can do ADLs but attend special classes because of cognitive difficulties or a learning deficit
4	Severe disability	In preschool-aged children, ADLs milestones below the 10th percentile and excessive dependence on others for activities of daily living In school-aged children, possibly severe impairment that prevents school attendance and dependence on others for ADLs In preschool-aged and school-aged children, possibly abnormal motor movements, including nonpurposeful, decorticate, or decerebrate responses to pain
5	Coma or vegetative state	Unawareness
6	Death	—
* Worst level of performance for any single criterion is used for categorizing. Deficits are scored only if they result from a neurologic disorder. Assessments are based on medical records or an interview with the caretaker.		
Adapted from Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr* 121(1):68-74, 1992. doi:10.1016/s0022-3476(05)82544-2		
ADLs = activities of daily living.		

Table 2: Functional Status Scale Score (from medical record review)(17)

	Normal (Score = 1)	Mild Dysfunction (Score = 2)	Moderate Dysfunction (Score = 3)	Severe Dysfunction (Score = 4)	Very Severe Dysfunction (Score = 5)
Mental status	Normal sleep/wake periods; appropriate responsiveness	Sleepy but arousable to noise/touch/movement and/or periods of social nonresponsiveness	Lethargic and/or irritable	Minimal arousal to stimuli (stupor)	Unresponsive, coma, and/or vegetative state
Sensory functioning	Intact hearing and vision and responsive to touch	Suspected hearing or vision loss	Not reactive to auditory stimuli or to visual stimuli	Not reactive to auditory stimuli and to visual stimuli	Abnormal responses to pain or touch
Communication	Appropriate noncrying vocalizations, interactive facial expressiveness, or gestures	Diminished vocalization, facial expression, and/or social responsiveness	Absence of attention-getting behavior	No demonstration of discomfort	Absence of communication
Motor functioning	Coordinated body movements, normal muscle control, and awareness of action and reason	1 limb functionally impaired	≥2 limbs functionally impaired	Poor head control	Diffuse spasticity, paralysis, or decerebrate/decorticate posturing
Feeding	All food taken by mouth with age-appropriate help	Nothing by mouth or need for age-inappropriate help with feeding	Oral and tube feedings	Parenteral nutrition with oral or tube feedings	All parenteral nutrition
Respiratory status	Room air and no artificial support or aids	Oxygen treatment and/or suctioning	Tracheostomy	Continuous positive airway pressure treatment for all or part of the day and/or mechanical ventilatory support for part of the day	Mechanical ventilatory support for all of the day and night

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary outcome is survival to hospital discharge with favorable neurologic outcome, defined as a PCPC score of 1-2 or no change from baseline. Baseline will be defined as the child's pre-

admission status. For those children hospitalized more than 90 days at the time of their CPR event, a new "baseline" will be assessed at within 30 days prior to the CPR event.

6.2 Secondary Endpoints

Secondary outcomes will be:

- Survival to discharge, a binary indicator of whether or not the subject was discharged alive.
- Return of spontaneous circulation (ROSC) >20 minutes, a binary indicator of whether or not the subject achieved adequate circulation via a native heartbeat.
- Return of circulation with extracorporeal membrane oxygenation (ECMO) support, a binary indicator that adequate circulation could only be achieved with ECMO support (i.e., E-CPR).
- Substantive new morbidity among survivors (increase in Functional Status Scale score ≥3).
- Intra-arrest cerebral oxygen saturation (%) as measured by Near Infrared Spectroscopy (NIRS) monitors, as part of standard clinical care in the pedRES-Q sites.
- Proportion of events 1) that achieve the DBP thresholds during CPR (14), and 2) with either hyperoxia (PaO2 >300 mmHg) or hypocarbia (PaCO2 <30 mmHg) in the post-arrest period (15).

6.3 Statistical Methods

For analysis, each CPR event will be divided into multiple 30-second epochs. An average of the following will be calculated: 1) ventilation rate (bpm); 2) $ETCO_2$ (mmHg); 3) compression rate; 4) arterial BPs; 5) chest compression fraction; 6) compression depth (mm); 7) exhaled tidal volume (mL); 8) minute ventilation (L/minute); 9) PIP (cm H2O); 10) PEEP (cm H2O); 11) % leak; and 12) cerebral oxygen saturation. An average of all epochs (event-level average) will be used in survival analyses.

Primary Objective (Efficacy of OPTI-VENT bundle)

The analysis of our primary outcome is based on all enrolled index events (first in-ICU cardiac arrest) excluding transition periods. For the primary analysis of the interventional trial, a mixed effect logistic regression model will be fit with our primary outcome as the dependent variable. The primary predictor will be treatment group, an indicator of whether the *OPTI-VENT* bundle was fully implemented prior to the arrest. Fixed covariates will be illness category, age, first documented rhythm, and time since trial start (to prevent confounding due to unrelated temporal changes in outcome) and time of day (weekday versus night or weekend). Etiology and severity of pre-existing lung disease will be evaluated as a confounder / effect modifier. Unit will be included as a random effect to account for heterogeneity in patient outcomes across ICUs and to accommodate clustering of patients within ICUs. The null hypothesis will be tested using the standard type III test for the fixed effect, and the p-value for the two-sided alternative will be presented.

Brief Description of Secondary Analytic Objectives

Ventilation Rate and Survival: We will explore the relationship between ventilation rate and survival using cubic splines and ROC curves. We will randomly divide our cohort into a derivation set (70%) and a validation set (30%). The derivation set will be used in an exploratory fashion to identify an optimal target using cubic splines and ROC curves in conjunction with clinical expertise. Then, the validation set will be used to validate the rate selected and to provide an unbiased estimate of the effect of achieving the target rate on outcome. Cubic splines will allow us to create a smooth curve of survival probability on the vertical axis against the event-level average ventilation rate on the horizontal axis, while controlling for potential confounders. We plan to stratify our analysis by age, and either adjust for / stratify by initial rhythm, immediate cause of arrest (e.g., respiratory deterioration, shock, sudden arrhythmia), severity (none, non-severe, severe) and etiology (none, obstructive, restrictive, mixed) of pre-existing lung disease, chest compression depth and rate (AHA compliant vs. not), and clinical site. If an alternative ventilation rate target is identified, we will quantify its association with survival outcomes using logistic regression models. Similarly, we will also explore the relationship between ventilation rate and 1) arterial diastolic BP and 2) exhaled carbon dioxide using linear regression models. For this analysis, individual epoch data will be used. Models will be adjusted for the same variables as above and account for the clustering of epochs from within events.

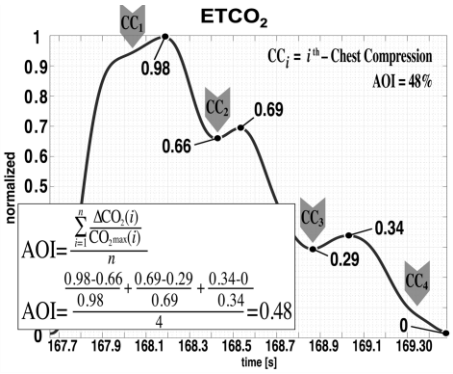


Figure 2: Airway Opening Index. The sum of the delta in ETCO2 divided by the max ETCO2 caused by each chest compression is averaged by the number of CCs. Higher values indicate greater airway patency.

Evaluation of Airway Opening Index: The calculation of Airway Opening Index will be done in the manner as described in Grieco et.al. (Figure 2). As with other variables, an average AOI for each 30-second CPR epoch will be calculated. For each event, the average of all the epochs will be calculated to be used in logistic regression survival analyses. Epoch-level data will be used in a similar fashion as described above to evaluate the association of AOI with intra-arrest physiology (e.g., blood pressure and $ETCO_2$) and delivered airway pressures (e.g., positive end expiratory pressure) in linear regression models, accounting for the clustering of epochs from within events. In addition to these standard statistical methods, this exploratory aim will involve the development of a multi-modal ML model. The input data will comprise both discrete values (e.g., demographic and clinical variables, $ETCO_2$, I/E ratio) and high-fidelity waveform data (e.g., arterial BP, capnogram). To evaluate model performance, we will use metrics such as accuracy, F1-score, and AUC-ROC.

6.4 Sample Size and Power

Primary Objective (Efficacy of OPTI-VENT bundle)

Based on pediRES-Q data, ~360 index CPR events are expected to occur annually. After excluding ~7 events/year that occur during transition periods, 1500 index events will be available for analysis. In our preliminary work, rates consistent with 2020 AHA Guidelines were associated with an improvement in survival with favorable neurologic outcome of >20 percentage points. Understanding that it is likely that the magnitude of the effect will be smaller in a multicenter study,

we have provided estimated power to detect a 12-16% improvement when the target rate is achieved compared to a baseline rate of survival with favorable neurologic outcome of 30% (data obtained from an existing pediRES-Q online real-time dashboard) when the target rate is not achieved. We also show the impact of the level of compliance with the target rate that we can achieve in the intervention group compared to a control group rate of 25%. We have assumed an intra-cluster correlation of 2% (based on our prior IHCA data). To ensure adequate power, we have included a pre-planned adaptive design. If after 12 months of enrollment, sites are enrolling ≤90% of expected, we will add 6 additional ICUs. If they are enrolling ≤75% of expected, we will add an additional 10 ICUs. As the pediRES-Q network has more than 50 active domestic / international sites, recruiting 10 sites is feasible. New sites if added will all begin in the control group starting at 14 months and will randomly be assigned a transition time according to a standard stepped-wedge design. Start-up within 2 months is feasible due to these sites starting in control, our plan for continuous enrollment monitoring, and the infrastructure of the pediRES-Q network (active IRBs and DUAs). Our design adaptation can also be used to mitigate power issues due to unexpectedly high baseline compliance in the control group or inability to achieve compliance training targets in the interventional group.

	Compliance			
Absolute improvement in survival with favorable neuro with compliance	**80%**	**85%**	**90%**	**95%**
12%	55%	63%	70%	76%
14%	68%	76%	82%	87%
16%	79%	86%	91%	94%

Secondary Analytic Objectives

Ventilation Rate and Survival: We conservatively estimate that ~20% of our subjects will not have usable ventilation data. Given the remaining cohort (~1200 patients), we will have more than 90% power to detect an improvement in survival from 30% to 40% if the ventilation rate is at target in 40%-60% of subjects. Given the absolute change in survival associated with the ventilation target from our preliminary data was >20%, we are conservatively powered for the primary objective of this aim. In subgroups as small as 350, we will have >80% power to detect an improvement in survival probability from 30% to 45%. Additionally, our preliminary data demonstrate that >25% of our patients with usable ventilation data will also have usable arterial BP data. With 300 subjects, we have >80% power to detect an association between ventilation rate and diastolic BP (assumptions: standard deviation of 10 mmHg for both; slope of line -2.10 mmHg / 10 bpm; ≥seven 30-second epochs of data per subject; within subject correlation of 0.60; two-sided alpha = 0.05).

Airway Opening Index: As this objective is exploratory in nature, a power calculation is not provided.

6.5 Interim Analysis

We plan to assemble a DSMB in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development for this study. The DSMB will be responsible for monitoring subject safety, accrual of study subjects, adherence to the study protocol, compliance with the *OPTI-VENT* training bundle, assessments of data quality, performance of individual clinical centers, and review of formal interim statistical analyses of treatment efficacy. The DSMB will be comprised of no less than five individuals and will include at least one independent PhD level statistician and one pediatric resuscitation scientist with expertise in pediatric resuscitation quality and interventional trials who will be proposed as the chair of the DSMB. This individual will not be

a previous collaborator of Dr. Sutton to avoid potential conflicts of interest. DSMB meetings will be scheduled as follows: full DSMB meeting after 1, 2, 3, and 4.5 years of enrollment; chair-only review at, 1.5, 2.5, and 3.5 years. Efficacy will be formally assessed at 2, 3, and 4.25 years. A symmetric, two-sided O'Brien-Fleming type boundary with overall alpha level set to 0.05 will be used as a guideline for stopping the study due to a difference between treatment arms. Stopping boundaries will be generated using symmetric monitoring boundaries, corresponding to alpha spending of 0.025 to detect a benefit and 0.025 to detect a harmful effect of treatment vs control. Lan-DeMets spending functions corresponding to O'Brien-Fleming type boundaries will be used. Monitoring boundaries will be set according to the proportion of total statistical information (information fraction) available in each interim analysis dataset. Due to challenges of estimating information fraction for this trial design, formal statistical stopping guidance will be provided at interim analysis timepoints according to the Haybittle-Peto boundary, with $\alpha = 0.001$. Futility analyses will not be performed for this minimal risk study because futility for the primary endpoint does not diminish the value of fully enrolling for other objectives. Adverse events will not be collected in this study as it is observational at the patient level (no therapeutic intervention at the patient level [no drug, no technology]).

7 STUDY INTERVENTION

7.1 Description

Description of the Resuscitation Bundle: The *OPTI-VENT* QI bundle consists of two main components: 1) provider education: physician, registered nurse, and respiratory therapist education (via scheduled existing educational or quality meetings) and 2) point-of-care ventilation guidance (CPR cue cards highlighting ventilation rate targets and introduction of a ventilation rate metronome [Figure 3]).

Provider Education / Point-of-Care Guidance: Point-of-care training will be conducted by pediRES-Q network site quality physician champions, leveraging their experience with high-risk patient identification. In short, *many of these network sites are already completing bedside preparation for cardiac arrest resuscitation in high-risk patients* (18). During this brief (<2 minute) bedside education, the educator will 1) review the CPR ventilation rate target, and 2) ensure the provider has their rate cue card on his/her person and knows how to activate the CPR ventilation rate metronome (Figure 3). Compliance will be defined as performance of at least 30 of these trainings per unit per month (~1 per day). Although our application focuses on ventilation rate, current Guidelines recommend that inflation pressures be targeted to "visible chest rise," without prescribing an actual peak inflating or end expiratory pressure. In an attempt to standardize this portion of care, we will leverage these two-minute trainings to review the patient's current ventilator settings as a starting point during CPR to ensure adequate chest rise. Post-arrest care ventilation and oxygenation goals (e.g., avoidance of hypocarbia) will also be reviewed. Additionally, an educational focus on CPR ventilation rates will be integrated into existing resuscitation education or quality meetings across all disciplines. A brief Microsoft PowerPoint presentation focusing on the benefits of CPR ventilation



Figure 3: Ventilation rate metronome on CHOP's CPR Monitoring Cart (standard clinical practice).

rate compliance will be developed and standardized for distribution across all sites. Past performance during actual cardiac arrests will also be presented to providers during the existing cardiac arrest debriefing programs that occur in all sites participating in this trial. To be compliant with this portion of the intervention, this must occur monthly. “Report cards” detailing unit-level performance will be generated by the University of Utah study data coordinating center and automatically emailed to the site PIs for review during their monthly presentations.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Adverse events will not be collected in this observational study.

8.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required), or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

The basis of this investigation is a hybrid between a parallel and stepped-wedge cluster-randomized trial. As in a parallel design, 4 randomly selected sites will be permanently assigned to enroll in the control group, and 4 others will be permanently assigned to enroll in the intervention group. The remaining 12 sites, as in a stepped-wedge design, will initially enroll in the control group but will be randomly assigned a time to begin implementing the intervention. In order to ensure roughly equal numbers of subjects in the intervention and control groups, and to ensure balance with respect to baseline pre-trial survival rates, the computer-generated randomization schedule will be selected from all possible configurations with sufficient expected balance in both expected enrollment and pre-trial survival rates.

9.2 Data Collection and Management

Limited patient, event, post-cardiac arrest care, and survival outcome data will be entered by each site into a protected electronic database which will be managed and stored using the research-focused electronic web-based data capture system REDCap, under an agreement with the software’s development consortium, led by Vanderbilt University. Data backup is performed nightly via a dedicated backup system. The backup environment is

maintained by a dedicated staff using dedicated resources. Access to the backup environment is restricted to Research Information Systems staff.

Statistical support will be provided by both the CHOP Data Science and Biostatistics Unit and the Data Coordinating Center (DCC) at the University of Utah School of Medicine, which provides data coordination and management services for a variety of national research networks. Limited data set exports will be shared with the DCC, the University of Utah, and Villanova University and may contain birth and service dates but will not contain names, MRNs, or similar identifying data.

a. Confidentiality. Site data coordinators may keep their completed paper-based data collection form (case report forms) in accordance with local IRB policies. Only the designated, trained site data coordinators and/or site investigators will input the data to REDCap. The minimum necessary PHI (i.e., subject name, MRN, date of birth and date of cardiac arrest events) will be collected by each site. However, the only patient information sent to the DCC will be date of birth and arrest (limited dataset) to enable proper data validation and accurate coding of data, such as the age of patients. The DCC will never obtain readily identifiable information from any of the participating sites. The DCC will protect strict confidentiality under the policy approved by IRB.

b. Security. The data is collected through a protected database portal (REDCap). The access is password protected. Each site investigator and/or data coordinator will have access to their local data only. Designated investigators at CHOP will have access only to the limited dataset.

c. Anonymization, de-identification or destruction. The minimum necessary PHI (subject name, MRN, date of birth and date of cardiac arrest events) will be collected.

i. PHI will not be reused or disclosed to any other person or entity, except: as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by HIPAA.

9.2.1 Data sources

REDCap will be abstracted by the University of Utah or CHOP to generate a coded dataset. Neither site will not have capability to identify events or patients at any study site. Readily identifiable information from any of the participating sites or investigators will never be requested. All other data are non-identifiable.

Standard cardiac arrest data (e.g., demographics, intra- and post-arrest physiologic variables, CPR quality variables) will be collected on all subjects, extracted from the electronic medical record, continuous bedside monitors, and other patient physiologic monitoring devices (e.g., NIRS). This limited dataset is in accordance with definitions of HIPAA.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies of the Children's Hospital of Philadelphia and HIPAA on subject privacy and

the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval or determination of exemption. Data use agreements already exist or will be obtained between CHOP/PI and the pediRES-Q sites / University of Utah DCC, and Villanova University before sharing a limited dataset.

PHI will not be reused or disclosed to any other person or entity, except: as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by HIPAA.

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

We plan to assemble a DSMB in collaboration with the Eunice Kennedy Schriver National Institute of Child Health and Human Development for this study. The DSMB is responsible for monitoring subject safety, accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual clinical centers, and review of formal interim statistical analyses of treatment efficacy. DSMB meetings will be scheduled as follows: full DSMB meeting at 1, 2, 3, and 4.5 years after enrollment; chair only review at, 1.5, 2.5, and 3.5 years. Efficacy will be formally assessed at 2, 3, and 4.25 years. A symmetric, two-sided O'Brien-Fleming type boundary with overall alpha level set to 0.05 will be used as a guideline for stopping the study due to a difference between treatment arms. Stopping boundaries will be generated using symmetric monitoring boundaries, corresponding to alpha spending of 0.025 to detect a benefit and 0.025 to detect a harmful effect of treatment vs control. Lan-DeMets spending functions corresponding to O'Brien-Fleming type boundaries will be used. Monitoring boundaries will be set according to the proportion of total statistical information (information fraction) available in each interim analysis dataset. Due to challenges of estimating information fraction for this trial design, formal statistical stopping guidance will be provided at interim analysis timepoints according to the Haybittle-Peto boundary, with $\alpha = 0.001$. Futility analyses will not be performed for this minimal risk study because futility for the primary endpoint does not diminish the value of fully enrolling for other objectives.

9.4.2 Risk Assessment

As this study is observational at the patient level, there is no more than minimal risk from the proposed study. Although there is a minor risk of loss of confidentiality, the risk is mitigated by data security procedures at CHOP, the University of Utah and Villanova University.

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy.

The risk to patient confidentiality of this study is further minimized by taking following steps:

1. Only minimally necessary data will be collected at the local level (subject name, MRN, date of birth and cardiac arrest event)

2. The minimally necessary PHI data to be entered into the REDCap database will be date of birth and date of arrest only.

3. The data entry will only be completed by the trained site data coordinator or site PI.

4. No individual site will have any access to another site's data besides the aggregated report. As noted above, the University of Utah and Villanova University will have access to the limited dataset.

5. DCC will strictly protect the limited dataset under the policy in accordance with HIPAA.

6. DCC will never request any readily identifiable information from any site

9.4.3 Potential Benefits of Trial Participation

There is the potential for direct benefit to the human subjects enrolled in this trial (i.e., CPR training will improve the quality of care they receive). Additionally, even if the *OPTI-VENT* training bundle fails to improve outcomes, future cardiac arrest victims have the potential to broadly benefit from the findings of this study, as evidenced-based ventilation targets for pediatric CPR will improve the care and outcomes of these patients. Implementation of these findings into future AHA Emergency Cardiovascular Care guidelines will influence the care provided to millions of patients around the world.

9.4.4 Risk-Benefit Assessment

Based on the discussion above and the lack of deviation from standard clinical care in this study, the benefits of this study outweigh the risks.

9.5 Recruitment Strategy

While patients cannot be recruited for this study (i.e., a cardiac arrest has to occur to be considered eligible), over the first 7 years of pediRES-Q network existence, trained clinical research assistants, clinical research coordinators, and site primary investigators have intensively screened for any eligible cardiac arrests. This has included local pager notification of cardiac arrests, email screening logs, daily morning screening rounds, and reviews of resuscitation records.

9.6 Informed Consent/Assent and HIPAA Authorization

9.6.1 Main Study

9.6.2 Waiver of Consent

Cardiac Arrest Subject: As this study is observational at the patient level, similar to other pediRES-Q network quality improvement interventional studies, a waiver of consent will be requested. This is also exactly similar to the consent process utilized for Dr. Sutton's now published *ICU-RESUS* interventional trial (*Journal of the American Medical Association*)(12) which implemented a similar training bundle to ICU providers, albeit focused on the chest compression aspect of CPR rather than assisted ventilation delivery. A waiver will be requested on the following factors: 1) This study poses no more than minimal risk (CPR training already exists at the participating hospitals and quality will be at least as good with OPTI-VENT implementation); 2) The waiver will not adversely affect the rights and welfare of the subjects (i.e., cardiac arrest patients undergoing CPR); 3) Obtaining informed consent would threaten the scientific validity of the study. The scientific validity of the study is dependent upon capturing all eligible events during the period of study, as one of the major goals is to associate ventilation data with survival outcomes; 4) This study involves no therapeutic intervention at the patient level (no drug, no technology), and there are no changes in accepted clinical practice; 5) Only a limited dataset will be shared with the University of Utah and Villanova

University. The minimal risk of loss of privacy will be mitigated by the substantial data management resources of the data management team at CHOP and the process by which they verify that only a limited dataset is sent to the University of Utah and Villanova University for analysis. As presently accepted in other pediRES-Q protocols, waiver of HIPAA authorization at the patient level will also be requested, as again, no identifying information will be transmitted outside of CHOP.

Healthcare Provider:

1) This study poses no more than minimal risk (CPR training already exists in ICUs and is a normal job-related responsibility and there are no links between the providers identify and their performance, either in the educational session or during actual patient care); 2) The research cannot be practically carried out without the waiver as it will be important to describe how the participating sites implemented the bundle. Additionally, consenting all providers would place undue burden on these healthcare providers who are caring for critically ill children who by definition have labor intensive care plan; 3) There are also no identifying links between the care providers and their resuscitation performance; 4) The waiver will not adversely affect the rights and welfare of the subjects as CPR training already exists in ICUs and is a normal job-related responsibility. The minimal risk of loss of privacy will be mitigated by the substantial data management resources of the data management team at CHOP and the process by which they verify that only a limited dataset is sent to the University of Utah and Villanova University for analysis. As presently accepted in other pediRES-Q protocols, waiver of HIPAA authorization at the patient level will also be requested, as again, no identifying information will be transmitted outside of CHOP.

10 PUBLICATION / DISSEMINATION

As a clinical trial, this study will be governed by the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, including but not limited to registering the trial on ClinicalTrials.gov and submitting clinical trial summary results information to ClinicalTrials.gov no later than 1 year following the end of study enrollment. Additionally, the study findings will be disseminated through the presentation at scientific meetings and publications. We will leverage the Society of Critical Care Medicine Annual Congress and the AHA's Resuscitation Science Symposium for knowledge dissemination. Only aggregate data, without individually identifiable information, will be published.

11 REFERENCES

1. Holmberg MJ, Ross CE, Fitzmaurice GM, Chan PS, Duval-Arnould J, Grossestreuer AV, et al. Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12(7):e005580.

2. Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, Chan PS, et al. Trends in survival after in-hospital cardiac arrest. *N Engl J Med*. 2012;367(20):1912-20.

3. Wolfe H, Zebuhr C, Topjian AA, Nishisaki A, Niles DE, Meaney PA, et al. Interdisciplinary ICU cardiac arrest debriefing improves survival outcomes*. *Crit Care Med*. 2014;42(7):1688-95.

4. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA.* 2006;295(1):50-7.

5. Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL, Jr., et al. Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2020;142(16_suppl_2):S469-S523.

6. Sutton RM, Reeder RW, Landis WP, Meert KL, Yates AR, Morgan RW, et al. Ventilation Rates and Pediatric In-Hospital Cardiac Arrest Survival Outcomes. *Crit Care Med.* 2019;47(11):1627-36.

7. Sutton RM, Niles D, Meaney PA, Aplenc R, French B, Abella BS, et al. Low-dose, high-frequency CPR training improves skill retention of in-hospital pediatric providers. *Pediatrics.* 2011;128(1):e145-51.

8. Chapman JD, Geneslaw AS, Babineau J, Sen AI. Improving Ventilation Rates During Pediatric Cardiopulmonary Resuscitation. *Pediatrics.* 2022;150(3).

9. Grieco DL, L JB, Drouet A, Telias I, Delisle S, Bronchti G, et al. Intrathoracic Airway Closure Impacts CO(2) Signal and Delivered Ventilation during Cardiopulmonary Resuscitation. *Am J Respir Crit Care Med.* 2019;199(6):728-37.

10. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. *Crit Care Med.* 2004;32(9 Suppl):S345-51.

11. Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, von Briesen C, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation.* 2004;109(16):1960-5.

12. The ICU-RESUS and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigator Groups, Sutton RM, Wolfe HA, Reeder RW, et al. Effect of Physiologic Point-of-Care Cardiopulmonary Resuscitation Training on Survival With Favorable Neurologic Outcome in Cardiac Arrest in Pediatric ICUs: A Randomized Clinical Trial. *JAMA.* 2022;327(10):934-45.

13. Reeder RW, Girling A, Wolfe H, Holubkov R, Berg RA, Naim MY, et al. Improving outcomes after pediatric cardiac arrest - the ICU-Resuscitation Project: study protocol for a randomized controlled trial. *Trials.* 2018;19(1):213.

14. Berg RA, Sutton RM, Reeder RW, Berger JT, Newth CJ, Carcillo JA, et al. Association Between Diastolic Blood Pressure During Pediatric In-Hospital Cardiopulmonary Resuscitation and Survival. *Circulation.* 2018;137(17):1784-95.

15. Del Castillo J, Lopez-Herce J, Matamoros M, Canadas S, Rodriguez-Calvo A, Cechetti C, et al. Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children. *Resuscitation.* 2012;83(12):1456-61.

16. Pollack MM, Holubkov R, Funai T, Clark A, Moler F, Shanley T, et al. Relationship between the functional status scale and the pediatric overall performance category and pediatric cerebral performance category scales. *JAMA Pediatr.* 2014;168(7):671-6.

17. Pollack MM, Holubkov R, Glass P, Dean JM, Meert KL, Zimmerman J, et al. Functional Status Scale: new pediatric outcome measure. *Pediatrics.* 2009;124(1):e18-28.

18. Niles DE, Dewan M, Zebuhr C, Wolfe H, Bonafide CP, Sutton RM, et al. A pragmatic checklist to identify pediatric ICU patients at risk for cardiac arrest or code bell activation. *Resuscitation.* 2016;99:33-7.

19. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the

international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation.* 2004;63(3):233-49.