

**Improving Outcomes from Pediatric Cardiac Arrest
(ICU-RESUS)
CPCCRN Protocol Number 068**

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute of Child Health and
Human Development (NICHD) & National Heart, Lung, and
Blood Institute (NHLBI)

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Improving Outcomes from Pediatric Cardiac Arrest

Short Title: ICU-RESUS
CPCCRN Protocol Number: 068

Lead Investigator and Author:
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Children's Hospital of Philadelphia

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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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Contents

1	Study Summary	7
1.1	Hypotheses	7
1.2	Specific Aims	8
1.3	Subject Eligibility, Accrual and Study Duration	8
2	Rationale and Background	9
3	Study Design and Intervention	11
3.1	Study Design Overview	11
3.2	Description of the Bundle	11
3.3	Compliance with the Intervention	14
4	Data Collection	14
4.1	Patient Characteristics	14
4.2	CPR Event Characteristics	17
4.3	Hemodynamic Variables	18
4.4	CPR Quality Variables	19
4.5	Post-CPR Care Variables	19
4.6	Pediatric Survival Outcome Data	20
4.7	Point of Care Training Data	20
5	Data Analysis	20
5.1	Specific Aim Analyses	21
5.2	Sample Size Calculations and Statistical Power	22
6	Data Management	22
6.1	Electronic Data Capture System	22
6.2	Study Monitoring	23
6.2.1	Site Monitoring Plan	23
6.2.2	Clinical Site Monitoring	23
6.2.3	Remote Monitoring	23
6.3	Data Coordinating Center	24
6.3.1	Data Center Description	24
6.3.2	Security and Confidentiality	26
6.4	Record Access	26
6.5	Echocardiogram Review	27

7	Protection of Human Subjects	27
7.1	Institutional Review Board (IRB) Approval	27
7.2	Potential Risks and Benefits	27
7.3	Protection Against Risks	28
7.4	Informed Consent	28
8	Data and Safety Monitoring Plan	29
8.1	Data Safety Monitoring Board (DSMB)	29
8.2	Adverse Event Reporting	29
9	Study Training	29
10	Regulatory Issues	30
10.1	Health Insurance Portability and Accountability Act	30
10.2	Inclusion of Women and Minorities	30
10.3	ClinicalTrials.gov Requirements	30
10.4	Retention of Records	30
10.5	Public Use Data Set	31

List of Figures

1	Schematic summary of overall study design	12
2	Point of care bedside refresher training.	13

Abstract

Pediatric cardiac arrest affects thousands of hospitalized children each year. While cardiac arrest survival outcomes have improved over the last decade, more than half of these children do not live to hospital discharge. As brain injury complicates care in those who do survive, the morbidity burden is substantial. Cardiopulmonary resuscitation (CPR), the medical procedure of providing chest compressions and ventilations during cardiac arrest, is life-saving, and higher-quality CPR leads to better outcomes. However, the quality of CPR, even in the pediatric intensive care unit (PICU) setting, is variable. Educational interventions to improve the quality of pediatric CPR have been developed and applied at the Children's Hospital of Philadelphia (CHOP) with a significant improvement in neurologically intact survival. The educational ICU-Resuscitation (ICU-RESUS) bundle includes: 1) frequent, short duration CPR training at the point-of-care in the ICU; and 2) interdisciplinary structured reviews of CPR events that emphasize patient-centric physiology, with discussion about how to optimize intra-arrest and post-arrest care.

The objective of this study is to determine the effectiveness of the ICU-RESUS bundle outside CHOP, utilizing the existing infrastructure of the National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN).

1 Study Summary

This is a parallel stepped-wedge hybrid cluster-randomized trial to assess the effect of the ICU-RESUS bundle on favorable neurological outcome of children after CPR events in an intensive care unit (ICU). ICU-RESUS will be implemented in all ICUs within a hospital simultaneously; the order in which hospitals implement the bundle is randomized. In addition to the 14 intensive care units (PICU and CICU) in the CPCCRN sites, four additional ICUs from outside CPCCRN will participate, for a total of 18 ICUs. The primary outcome is survival to hospital discharge with favorable neurological outcome.

1.1 Hypotheses

The hypotheses of this study are:

1. There will be at least a 27% relative increase in survival with favorable neurological outcome at hospital discharge following implementation of the ICU-RESUS bundle.
2. There will be at least a 50% relative increase in the proportion of minutes with high quality CPR provided during ICU CPR events.
3. LV systolic dysfunction (defined as LV global longitudinal strain greater than 18%) will be associated with lower rates of survival to hospital discharge and survival with good neurobehavioral outcome (PCPC 1–2 or no change from baseline). LV systolic dysfunction post-arrest will be less common among patients who receive high-quality CPR as defined by arterial blood pressure during CPR (diastolic blood pressure ≥ 25 mmHg in infants or ≥ 30 mmHg in older children).
4. RV systolic dysfunction (defined as RV global longitudinal strain greater than 18%) will be associated with lower rates of survival to hospital discharge and survival with good neurobehavioral outcome (PCPC 1–2 or no change from baseline). RV systolic dysfunction post-arrest will be less common among patients who receive high-quality CPR as defined by arterial blood pressure during CPR (diastolic blood pressure ≥ 25 mmHg in infants or ≥ 30 mmHg in older children).

1.2 Specific Aims

This project has the following Specific & Ancillary Aims:

Specific Aim 1. Evaluate the effectiveness of the ICU-RESUS interventional bundle to improve survival with favorable neurological outcome at hospital discharge in children treated for an ICU CPR event.

Specific Aim 2. Evaluate the effectiveness of the ICU-RESUS interventional bundle to improve the quality of CPR provided by ICU healthcare providers for children during an ICU CPR event.

Ancillary Aim 1. Evaluate end-tidal carbon dioxide (ETCO₂) as a non-invasive CPR quality monitor among children receiving at least 1 minute of CPR in a CPCCRN intensive care unit (ICU).

Ancillary Aim 2. Using novel machine learning classification algorithms, evaluate the PhotoPlethysmoGraph (PPG) waveform and other candidate physiologic waveforms as non-invasive CPR quality monitors.

Ancillary Aim 3. To determine the association between LV systolic dysfunction within 48 hours of IHCA and survival.

Ancillary Aim 4. To determine the association between RV systolic dysfunction within 48 hours of IHCA and survival.

Ancillary Aim 5. Identify implementation strategies used by sites, as well as facilitators and barriers to implementation of the ICU-RESUS interventions. (Interviews: site leaders).

Sub Aim 1: Identify changes in resuscitation care that occurred at the site as the result of the ICU-RESUS intervention.

Ancillary Aim 6. Measure the acceptability and appropriateness of the ICU-RESUS interventions as experienced by participants at high and low performing sites. (Focus Groups: site participants).

1.3 Subject Eligibility, Accrual and Study Duration

Inclusion criteria are:

1. Age $\geq$ 37 weeks and $\leq$ 18 years of age; AND

2. Received CPR in the ICU setting.

Exclusion criteria are:

1. Pre-existing terminal illness and patient not expected to survive to hospital discharge.
2. Lack of commitment to aggressive ICU therapies.
3. Brain death determination prior to CPR event.
4. First CPR event associated with this hospital admission was an out-of-hospital CPR event.

Subject enrollment at all sites will occur over 4.5 years. The anticipated total number of patients enrolled is 1540, with approximately 770 prior to and 770 after implementation.

2 Rationale and Background

Pediatric cardiac arrest is a serious life-threatening problem affecting thousands of hospitalized children each year.¹⁻³ It is the end result of many disease processes affecting the cardiovascular and pulmonary systems.⁴⁻⁶ A CPR event that occurs in a hospitalized child most often happens in an intensive care unit (ICU),³ and is caused by progressive respiratory failure and/or circulatory shock.^{1, 3, 4} While CPR event survival outcomes have improved over the last decade,^{3, 5} more than half of these children will not live to hospital discharge.^{3, 5, 6} As adverse neurological sequelae complicate care in those who do survive,^{5, 6} the morbidity burden to these children is substantial.

Cardiopulmonary resuscitation (CPR) is the act of providing chest compressions and ventilations during a cardiac arrest with the goal of circulating metabolic substrate to vital body organs.⁷ Even for healthcare providers, providing high quality CPR is difficult. Inadequate compression rate,⁸⁻¹³ depth,^{11, 12, 14-17} and long interruptions in CPR are common.^{13, 14, 18-23} CPR event outcome is directly associated with the quality of resuscitation.²⁴⁻²⁶ As efforts to improve resuscitative care with conventional training methods have not been successful,²⁷⁻³¹ novel educational interventions to improve pediatric CPR quality, and ultimately, outcomes, are needed.

In a single-center efficacy educational trial at the Children's Hospital of Philadelphia (CHOP), an "ICU-Resuscitation (ICU-RESUS)" bundle consisting of: 1) point-of-care bedside CPR skill training on manikins; and 2) interdisciplinary post-CPR event debriefing³² improved CPR quality and CPR event survival outcome.³³ The success of the ICU-RESUS educational bundle was attributed to the incorporation of patient-centric

physiology into the intervention, and further, to the inclusion of all ICU providers in the educational debriefings, whether or not they participated in the actual event under review. This novel approach of emphasizing patient physiology and targeting all providers who may have to perform CPR at a future event has had broad impact and changed resuscitation care across the ICU clinical environment at CHOP. The objective of this study is to determine the effectiveness of the ICU-RESUS bundle outside CHOP, utilizing the existing infrastructure of the National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN).

Ancillary Aim 3–4:

Post-cardiac arrest syndrome is characterized by the triad of systemic ischemia and reperfusion, brain injury, and myocardial dysfunction. Left ventricular (LV) systolic dysfunction as measured by conventional echocardiographic methods within 24 hours of pediatric out-of-hospital cardiac arrest (OHCA) and hypotension within 6 hours of pediatric cardiac arrest are associated with mortality.^{34, 35} In adult OHCA patients, RV systolic dysfunction is predictive of worse survival and worse neurologic outcome independent of LV systolic dysfunction.³⁶ The prevalence and importance of LV and RV systolic dysfunction following successful resuscitation after pediatric in-hospital cardiac arrest (IHCA) are unknown.

Ancillary Aim 5–6:

Preliminary data show that sites in ICU-RESUS had varied implementation of clinical event debriefing, which may affect the site level impact of the intervention. Also, previous studies of debriefing interventions have failed to evaluate the participants acceptance of this intervention and understand how site level psychological safety impacts the acceptance of the intervention. We hope to identify the factors that contribute to the successful implementation of the ICU-Resus intervention. In this study, we will examine how ICU-Resus has been implemented at different sites with the goal of identifying successful practices that can be used at future hospitals. We will draw on the positive deviance framework, which is increasingly used in patient safety research to understand why particular sites are successful at adopting an intervention and learning from these sites to reproduce the intervention elsewhere. We will utilize interviews with site leaders (site PI, nursing lead, research coordinator) from all sites, as well as focus groups with site participants (RNs, MDs, RTs) of high and low performing sites to understand the implementation and acceptance of the ICU-RESUS interventions.

3 Study Design and Intervention

3.1 Study Design Overview

The trial design includes 18 intensive care units from 10 hospitals. All ICUs within the same hospital will transition at the same time. Hospitals 1 and 2 will begin implementation (transition to the intervention) prior to the beginning of patient enrollment, and Hospitals 9 and 10 will not implement the bundle during the study. The other hospitals will be implemented on a schedule that divides the anticipated number of patients evenly between pre and post bundle implementation, accrued over 4.5 years. The order of hospitals (1 through 10) will be randomized and sites will be notified eight to 12 weeks prior to scheduled implementation, to facilitate training of those individuals who will be leading the point of care training and debriefing programs at the sites. Data collection will be continuous for the entire 4.5 years at all hospitals, but data from the transition periods will not be used in analysis. Figure 1 summarizes the overall study design.

3.2 Description of the Bundle

The ICU-RESUS bundle includes frequent point-of-care bedside refresher training and physiology-centered debriefings of CPR events. A mobile cart with CPR mannikin will be used to provide training within the ICU (Figure 2 on page 13). Bedside training will include reminding the clinical providers of the American Heart Association (AHA) recommended targets for CPR performance.

The targets for CPR performance in all patients are:

- Depth 40 mm for age < 1 year and 50 mm for older patients.
- Rate ≥ 100 and ≤ 120 per minute
- Chest compression fraction $\geq 80\%$

In addition to educating clinicians about these standard targets, when the clinician's patient has an arterial line or an end tidal CO₂ monitor, the clinician will receive supplemental information about optimizing CPR with these two additional physiological variables. The targets for these monitors are:

- Systolic BP >60 mmHg for neonates, >80 mmHg for infants, and >100mmHg for older patients.
- ETCO₂ > 25 mmHg.

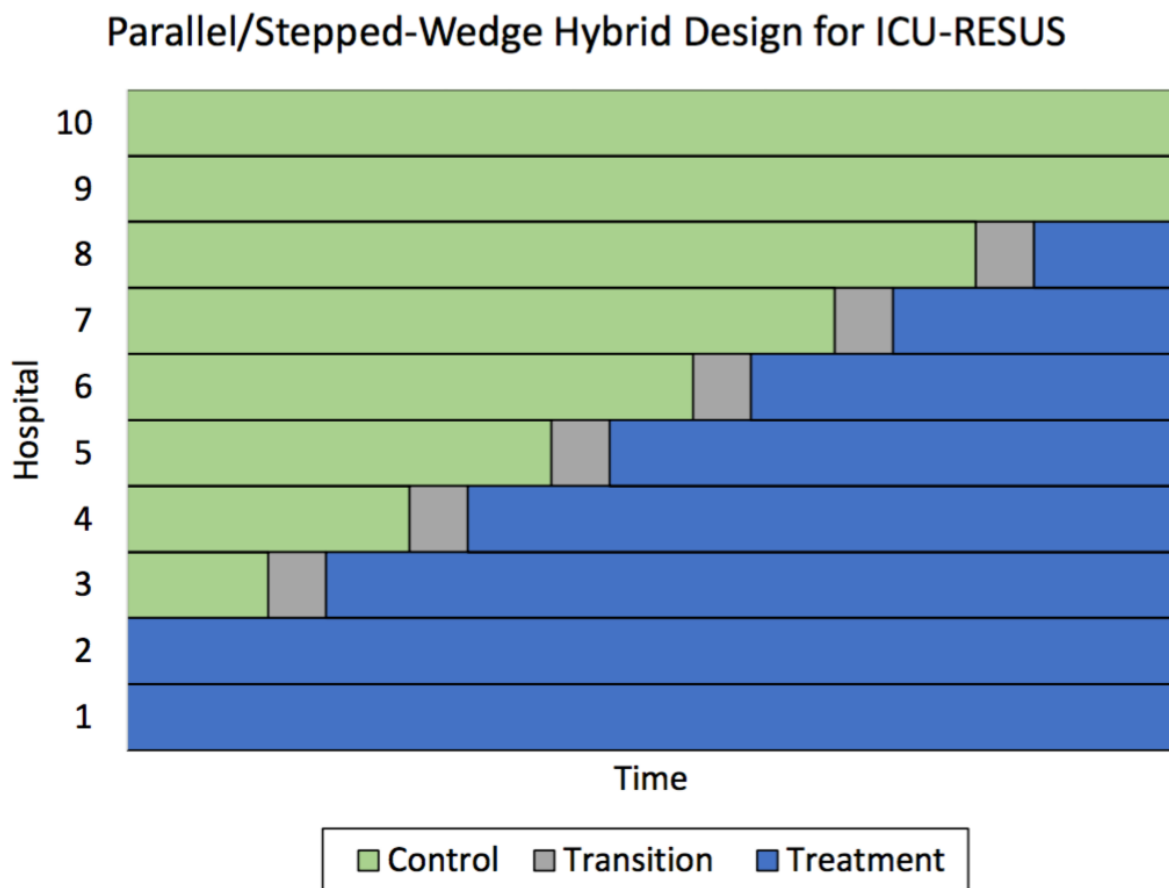


Figure 1: Schematic summary of overall study design



Figure 2: Point of care bedside refresher training.

Research staff will be notified for each real CPR event that occurs in the ICU, and will have a brief conversation with the bedside nurse of the patient as soon as feasible (goal is within 1 hour of the event). The purpose of this conversation is to determine if a prospective plan has been developed to monitor for and treat hypotension and fever.

At least once per month, CPR event debriefing sessions will be held within three weeks of actual CPR event. If no CPR events have occurred during the period, sites will have access to de-identified cases and CPR best practice slides to facilitate debriefing. All clinical disciplines (nurses, nurse practitioners, respiratory therapists, residents, fellows and attending physicians) will be invited to these sessions, including providers who did not participate in the event being reviewed. The debriefing will concentrate on subject specific clinical data as the overall performance is reviewed:

- Patient history
- Pertinent pre-arrest data with a focus on physiology (was there identifiable patient deterioration prior to arrest?)
- Quantitative CPR quality data with a focus on intra-arrest physiology
- Post-arrest care with a focus on post-arrest physiology
- Patient outcomes
- Systems failures / improvements.

The ICU-RESUS bundled debriefings will be approximately 60 minutes in duration. These debriefings will also highlight identification and treatment of post-arrest hypotension and fever, as these are possible modifiable risk factors to improve survival of children with post-CPR events.

3.3 Compliance with the Intervention

All point of care training and debriefing sessions will be tracked to assure compliance with the intervention. There are approximately 60 trainings per month; sites will be compliant if at least 80% (48) are completed and of those completed, at least 60% meet the training targets detailed above. Sites will be judged compliant with the debriefings if at least 75% (9/12) are completed during each 12 month period of intervention.

4 Data Collection

The specific question and choice set wording that is included below may not represent the final data collection implemented in the electronic data capture system. If substantively new data elements are added to the study, this protocol will be amended.

4.1 Patient Characteristics

- Date of birth
- Sex
- Race/Ethnicity
- Height & weight
- Baseline Pediatric Cerebral Performance Category (PCPC)
- Baseline Functional Status Score (FSS)
- Out-of-hospital cardiac arrest that led to this hospital admission (Y/N)
- Date and time of hospital admission
- Date and time of ICU admission
- Illness Category
 - Medical cardiac
 - Medical non-cardiac
 - Surgical cardiac
 - Surgical non-cardiac
 - Trauma

- Pre-existing conditions (at time of CPR event):
 - Respiratory insufficiency (Y/N)
 - Hypotension (Y/N)
 - Congestive heart failure (Y/N)
 - Pneumonia (Y/N)
 - Sepsis (Y/N)
 - Trauma (Y/N)
 - Renal insufficiency (Y/N)
 - Malignancy (Y/N)
 - Congenital heart disease (Y/N):
 - If yes, single ventricle (Y/N)
 - * If yes, specify anatomy at time of CPR event:
 - Preoperative
 - Norwood with modified BT Shunt
 - Norwood with Sano Modification
 - Bi-directional Glenn (Hemi-Fontan)
 - Fontan
 - Pulmonary Hypertension
 - * As active hospital problem OR
 - * Treatment with any of the following drugs:
 - Treprostinil
 - Eproprostinil
 - Iloprost
 - Selexipag
 - Ambrisentan
 - Sitaxsentan
 - Bosentan
 - Macisentan
 - Sildenafil
 - Tadalafil
 - Vardenafil
 - Riociguat
 - * Active order for inhaled iNO? (If yes, reason for iNO)
 - Primary respiratory dysfunction (select one)
 - Acute lung injury/ARDS (non-pulmonary etiology)
 - Acute lung injury/ARDS (sepsis)
 - Asthma
 - Bronchiolitis (not RSV)

- Pneumonia (aspiration)
 - Pneumonia (bacterial)
 - Pneumonia (viral other than RSV)
 - RSV (pneumonia/bronchiolitis/pneumonitis)
- Primary cardiac dysfunction (select one)
 - Cardiomyopathy
 - Cardiomyopathy s/p ECMO or VAD placement
 - Congenital heart disease
 - Heart transplant (post-operative)
 - Pulmonary hypertension (pre-existing)
- Vasoactive Inotropic Score (VIS) (−2 hours preceding CPR event; +6 and +24 hours post ROSC)
 - Dopamine (μ /kg/min)
 - Dobutamine (μ /kg/min)
 - Nitroprusside (μ /kg/min)
 - Milrinone (μ /kg/min)
 - Epinephrine (μ /kg/min)
 - Norepinephrine (μ /kg/min)
 - Phenylephrine (μ /kg/min)
 - Vasopressin (specify units)
- PRISM IV (−6 to −2 hours preceding CPR Event)
 - Lowest blood pressure (mmHg)
 - Highest heart rate (bpm)
 - Lowest temperature ($^{\circ}$)
 - Highest temperature ($^{\circ}$)
 - Pupillary reflexes
 - Glasgow Coma Score eye response
 - Glasgow Coma Score verbal response
 - Glasgow Coma Score motor response
 - Intubated at time of Glasgow Coma Score (Y/N)
 - Lowest pH
 - Highest pH
 - Lowest PaO₂ (mmHg)
 - Highest PCO₂ (mmHg)
 - Lowest total CO₂ (mmol/L)
 - Highest total CO₂ (mmol/L)

- Highest serum glucose (mg/dL)
- Highest serum potassium (mmol/L)
- Highest creatinine (mg/dL)
- Highest blood urea nitrogen (BUN) (mmol/L)
- Lowest white blood cell count (WBC) (10^3 /microliter)
- Lowest platelet count (10^3 /microliter)
- Highest PT (seconds)
- Highest PTT (seconds)

4.2 CPR Event Characteristics

- Date and Time of start of chest compressions
- Location of event (PICU/CICU)
- Interventions in place at time of event (Y/N)
 - Vascular access (Y/N)
 - Arterial catheter (Y/N)
 - Central venous catheter (Y/N)
 - Vasoactive infusion (Y/N)
 - Invasive mechanical ventilation (Y/N)
 - ET CO_2 monitoring (Y/N)
 - Non-invasive ventilation (Y/N)
 - Airway cuffed (Y/N)
- Immediate cause of CPR event:
 - Hypotension
 - Respiratory decompensation
 - Arrhythmia (VF, VT, SVT)
 - Cyanosis without respiratory decompensation
- Event during or within 20 minutes of endotracheal intubation (Y/N)
- Was the cardiac arrest witnessed (Y/N)
- Time from start of compressions to CPR quality sensor placement (e.g., pad, puck)
- First documented rhythm requiring CPR:
 - Ventricular fibrillation (VF)
 - Ventricular tachycardia (VT)
 - Pulseless electrical activity (PEA)
 - Asystole

- Bradycardia with pulses
- Open or closed sternum at onset of CPR
- Date and time sternum opened during CPR
- Time of first shockable rhythm
- Pre-shock pause lapsed time
- Time of first attempted defibrillation for shockable rhythm
- Time of first administration of a vasopressor medication bolus
- Pharmacologic interventions during CPR:
 - Epinephrine
 - * Total number of epinephrine doses
 - Atropine
 - Calcium
 - Sodium bicarbonate
 - Vasopressin
 - Amiodarone
 - Lidocaine
 - Fluid bolus
 - Other (specify)
- Date, time and dose of vasopressors
- Date and time of end of chest compressions
- Outcome of CPR:
 - ROSC $\geq$ 20 minutes
 - Transitioned to ECMO
 - Died
- Pre- and post-resuscitation echocardiograms, uploaded for data abstraction

4.3 Hemodynamic Variables

Waveforms of the following variables will be provided up to the first 20 minutes of chest compressions.

- Systolic arterial blood pressure (mmHg)
- Diastolic arterial blood pressure (mmHg)
- Central venous pressure/right atrial pressure (mmHg)
- ETCO₂
- Electrocardiogram (bedside monitor)

- Impedance plethysmography (bedside monitor)
- Pulse oximetry (bedside monitor)

4.4 CPR Quality Variables

An optional component of this protocol involves obtaining quality of CPR data from defibrillators that capture data such as depth of chest compression. Data will be accepted from participating sites that have chest compression quality measurement capability (e.g., Zoll R-series, Philips MRx, Physiocontrol LIFEPAK 20e). The following CPR quality variables will be calculated:

- Depth (mm)
- Rate (min^{-1})
- Chest compression fraction (CCF)
- Leaning (release velocity [m^2] or force [g])

4.5 Post-CPR Care Variables

The following variables will be collected during the first 24 hours after a CPR event if the subject has return of spontaneous circulation (ROSC) or was transitioned to ECMO. The highest value and lowest value will be documented for each variable below (unless otherwise indicated)

- Systolic arterial blood pressure (mmHg)
- Diastolic arterial blood pressure (mmHg)
- Temperature ($^{\circ}\text{C}$)
- Arterial PaO_2 (mmHg)
- PCO_2 (mmHg)
- pH
- Highest lactate (mmol/L)
- Glucose (mg/dL)
- Pulse oximetry (SpO_2)
- Required ECMO support for entire 24 hours (Y/N)
- Targeted temperature management (Y/N)
 - Goal max temperature:
 - * $32^{\circ} - 34^{\circ}\text{C}$

- * 34° – 37.5°C
- * Other (specify)
- EEG (Y/N)
 - If yes, de-identified report for first 72 hours post arrest
- Head imaging (Y/N)
 - If yes, de-identified report for first 168 hours post arrest (7 days)
- Limitations of technological support post CPR during hospitalization (Y/N)
 - If yes,
 - * Limitations in mechanical ventilation (Y/N)
 - * cardiac/chest compressions (Y/N)
 - * vasoactive medications (Y/N)
 - * ECMO (Y/N)
 - * VAD (Y/N)

4.6 Pediatric Survival Outcome Data

- Date and time of ICU discharge
- Date and time of hospital discharge
- Vital status at time of hospital discharge
 - Alive
 - Dead
- Death date and time
- PCPC at hospital discharge
- FSS at hospital discharge

4.7 Point of Care Training Data

When point of care training is conducted, each provider who is trained will record the date, time, training score, and the number of days since they last received point of care training. This is intended to measure breadth of training across the ICU staff.

5 Data Analysis

The hypotheses of this study are:

1. There will be at least a 27% relative increase in survival with favorable neurological outcome at hospital discharge following implementation of the ICU-RESUS bundle.
2. There will be at least a 50% relative increase in the proportion of minutes with high quality CPR provided during ICU CPR events.
3. LV systolic dysfunction (defined as LV global longitudinal strain greater than 18%) will be associated with lower rates of survival to hospital discharge and survival with good neurobehavioral outcome (PCPC 1–2 or no change from baseline). LV systolic dysfunction post-arrest will be less common among patients who receive high-quality CPR as defined by arterial blood pressure during CPR (diastolic blood pressure ≥ 25 mmHg in infants or ≥ 30 mmHg in older children).
4. RV systolic dysfunction (defined as RV global longitudinal strain greater than 18%) will be associated with lower rates of survival to hospital discharge and survival with good neurobehavioral outcome (PCPC 1–2 or no change from baseline). RV systolic dysfunction post-arrest will be less common among patients who receive high-quality CPR as defined by arterial blood pressure during CPR (diastolic blood pressure ≥ 25 mmHg in infants or ≥ 30 mmHg in older children).

5.1 Specific Aim Analyses

Specific Aim 1. Evaluate the effectiveness of the ICU-RESUS interventional bundle to improve survival with favorable neurological outcome at hospital discharge in children treated for an ICU CPR event.

The binary primary endpoint is survival to hospital discharge with favorable neurologic outcome. Favorable neurologic outcome is defined as a PCPC score less than 4 (i.e. no more than moderate disability), or a PCPC that is no worse than the baseline PCPC prior to arrest. This baseline should be based on the most recent measurable PCPC prior to arrest.

CPR events occurring prior to the roll-out of the ICU-RESUS bundle are analyzed as the control group. CPR events occurring during the transition period will not be included in this analysis. CPR events after the transition period will be analyzed as the treatment group. The effect of the ICU-RESUS intervention on the primary endpoint will be assessed with a generalized linear mixed model (logistic regression) that includes important covariates such as age, type of ICU, and severity of illness.

Specific Aim 2. Evaluate the effectiveness of the ICU-RESUS interventional bundle to improve the quality of CPR provided by ICU healthcare providers for children during an ICU CPR event.

The effect of the ICU-RESUS bundle on CPR quality will be assessed with regression models that include covariates such as age, type of ICU, and severity of illness. CPR quality measures include adequate SBP, adequate compression rate, adequate CCF, and high-quality CPR (adequate SBP, rate, and CCF). SBP is considered adequate if it is, on average, > 60 for neonates, > 80 mmHg for infants, or > 100 mmHg for older patients. An average chest compression rate between 100 and 120 per minute and a CCF $> 80\%$ are considered adequate.

5.2 Sample Size Calculations and Statistical Power

In the single-center study at CHOP, the treatment bundle improved survival with favorable neurologic outcome 21% (absolute), going from 29% survival to 50% survival. In previous CPCCRN studies, survival after CPR events is approximately 40%. This study is designed to detect an improvement from 40% survival to 51% survival with 82% power. Power calculations for parallel stepped-wedge hybrid cluster randomized trials require an estimate of intraclass correlation, which was measured at 0.03 in the in-hospital Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial (results not yet published). The required number of patients is 1540 over 4.5 years.

6 Data Management

The investigators and study staff are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. Study worksheets are to be completed in a neat, legible manner to ensure accurate interpretation of data. Any corrections or changes on the worksheets when made, the original entry should be crossed out using a single line, and must be dated and initialed by the individual making the change. The original entry will not be erased or overwritten. Additionally, the Electronic Health Record (EHR) serves as source documentation for this study. Sites are responsible to maintain access or copies of EHR source data in addition to worksheets.

6.1 Electronic Data Capture System

Data from this study will be entered into an electronic data capture (EDC) system used by the Data Coordinating Center (DCC) at the University of Utah. This system provides secure user access via the Internet, and maintains an audit log for all study events and data.

6.2 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Site monitoring is critical to this process. Site monitoring has been a very effective tool for maintaining data quality in previous CPCCRN studies, and we will utilize this process to ensure excellent quality data in this study. The site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Site monitors must be provided with full access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

6.2.1 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from this protocol, will outline specific details of monitoring. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, 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. Remote site monitoring schedules will be determined by the Data Coordinating Center in coordination with the study principal investigator.

6.2.2 Clinical Site Monitoring

Site monitoring visits may be performed 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. Due to the cost of physical site visits and budgetary constraints of this study, most site monitoring is anticipated to be remote monitoring.

6.2.3 Remote Monitoring

Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This may require remote access by Data Coordinating Center (DCC) staff to the local Electronic Health Record (EHR) and/or local site staff review of EHR in real-time via screen share with DCC staff. Monitoring may also include, uploading de-identified copies of specific parts of the medical record, patient study file, regulatory documentation, or other source documents to the Data Coordinating Center

staff, who review those materials against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. Additionally, review of complete consent forms will be conducted to ensure compliance with consent documentation. The Data Coordinating Center 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.

6.3 Data Coordinating Center

6.3.1 Data Center Description

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center completed in 2013. The data center facility supports more than 1200 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 95% of its environment. The virtual environment consists of more than 160 virtual servers and nearly 20 physical servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.

- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware or software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages over 50 terabytes of data. The storage solution consists of Dell's EqualLogic PS Series Storage system for providing a virtualized storage area network (SAN). Some of the benefits that are realized through this technology are:

- storage architecture is no longer be a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of SAN disk will be much easier; and most important,
- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. DCC storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

DCC information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

6.3.2 Security and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the SSL protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2008 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency 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 of our information systems, before access is provided.

6.4 Record Access

The medical record and study files 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, and the Institutional Review Board (IRB) for each study site.

6.5 Echocardiogram Review

To accomplished aims related to echocardiograms, echocardiograms will be re-analyzed using conventional and strain echocardiography by investigators at CHOP blinded to clinical information. The intent is to analyze up to 1 pre-arrest echocardiogram if performed within 1 month of the arrest (closest to arrest will be selected if there are multiple pre-arrest studies) and up to 2 post-arrest echocardiograms in the 48 hour period following ROSC/ROC. Qualifying and deidentified echocardiograms will be uploaded to a central repository located at CHOP. At the individual sites, these echocardiograms will be scrubbed of any identifying information by renaming the file to the ICU-RESUS study OpenClinica ID (OCID). The University of Utah will provide a data export of ICU-RESUS study data to the CHOP investigators that will contain relevant clinical data as it pertains to LV and RV function evaluation (e.g., etiology of arrest, pre-arrest PRISM, initial rhythm, interventions during the arrest, vasoactive scores). These clinical data will be linked to the echocardiography parameters for analysis by the CHOP study team using the OCID. Through this process, the CHOP study team will not interact with any identifying data.

7 Protection of Human Subjects

7.1 Institutional Review Board (IRB) Approval

Institutional Review Board approval will be obtained for all sites and the Data Coordinating Center prior to enrollment of subjects in this study. The Data Coordinating Center will track IRB approval status at all sites and will not permit subject enrollment without documentation of continued IRB approval throughout the study.

7.2 Potential Risks and Benefits

CPR event Subject: As the ICU-RESUS intervention is targeted to ICU care providers, this is essentially an observational study at the level of the CPR event patient. Therefore, this study poses no more than minimal risk (i.e., CPR training already exists in the CPCCRN ICUs and resuscitation quality should be at least as good with ICU-RESUS implementation). The minimal risk of loss of privacy is mitigated by: 1) the substantial

data management resources at the DCC; and 2) the validation process by which the DCC verifies that no identifiable patient data is entered into the analytic database.

Healthcare Provider: This study also poses no more than minimal risk to the healthcare providers who will be targeted with the ICU-RESUS educational bundle. CPR training already exists in ICUs and is a normal job related responsibility. This is an educational / quality improvement intervention. Finally, there are no identifying links between the care providers and the quality of their point-of-care training or actual resuscitation performance.

7.3 Protection Against Risks

Data security and confidentiality procedures at the DCC have been described. Patient information is sent to the DCC to enable proper data validation and accurate coding of data, such as the age of patients. To prepare the analytical database, the DCC will recode all such patient identifiers, and create a de-identified data set in accordance with definitions of HIPAA. This analytical database will be the only one available for the analysis of the current and future derivative studies.

7.4 Informed Consent

Waiver of patient consent is requested for this non-therapeutic interventional study. The justification for waiver of consent is based on the following factors:

1. 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 accurately describe survival outcomes after CPR.
2. The study involves no therapeutic interventions.
3. The minimal risk of loss of privacy is mitigated by secure data management at the DCC.

Waiver of consent is also requested for the healthcare providers for this educational study. The study poses no more than minimal risk (CPR training already exists in ICUs and is a normal job related responsibility). The waiver will not adversely affect the rights or welfare of the healthcare providers as there are no identifying links between

the care providers and the quality of their point-of-care training or actual resuscitation performance. This is an educational / quality improvement intervention.

8 Data and Safety Monitoring Plan

8.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB). The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as applicable. The purpose of the DSMB is to advise the National Heart, Lung, and Blood Institute (NHLBI) and 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 clinical centers, and review of formal interim statistical analyses of treatment efficacy.

The DCC will send confidential reports relating to these topics to the DSMB members prior to each DSMB meeting. Interim analyses are anticipated after approximately 1/2 and after 3/4 of the projected total number of events have occurred. NHLBI will staff the DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by DSMB Executive Secretary provided by NHLBI. These closed minutes will not be available outside the DSMB prior to the end of the study. The DSMB Executive Secretary will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. After approval of this summary by NHLBI, the document will be distributed to the sites and can be submitted to relevant IRBs of the participating institutions.

8.2 Adverse Event Reporting

Adverse events are not being recorded in this study as there is no therapeutic intervention.

9 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in-depth explanations regarding study procedures,

clinical care, data entry procedures, quality assurance, and site monitoring. 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 and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the study investigator (Dr. Sutton), will be the main contact for study questions.

10 Regulatory Issues

10.1 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude these specific dates.

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

For purposes of the DCC handling potential protected health information (PHI) and producing the 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.

10.2 Inclusion of Women and Minorities

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

10.3 ClinicalTrials.gov Requirements

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

10.4 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion

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

10.5 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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