Pediatric Intensive Care Quality of CPR (PICqCPR)
CPCCRN Protocol Number 041

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD)

Protocol Version 1.03
Version Date: January 28, 2015
Printing Date: January 28, 2015

This protocol is CPCCRN Protocol Number 041, and the lead CPCCRN investigator for this protocol is Robert Berg, M.D., Children's Hospital of Philadelphia.

The CPCCRN Clinical Centers participating in this study are the Children's Hospital of Colorado, Children's Hospital of Los Angeles, Children's Hospital of Michigan, Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Children's National Medical Center, Nationwide Children's Hospital, Phoenix Children's Hospital, University of California at San Francisco, and the University of Michigan, and are supported by Cooperative Agreements UG1-HD083171, U10-HD050012, UG1-HD050096, UG1-HD063108, UG1-HD049983, UG1-HD049981, UG1-HD083170, U10-HD063114, UG1-HD083166, and U10-HD063106, respectively, from the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD).

This document was prepared by the CPCCRN Data Coordinating Center located at the University of Utah School of Medicine, Salt Lake City, Utah. The CPCCRN Data Coordinating Center at the University of Utah is supported by Cooperative Agreement U01-HD049934 from the National Institute for Child Health and Human Development (NICHD). The document was written and typeset using LaTeX 2_ε.

PROTOCOL TITLE:

Pediatric Intensive Care Quality of CPR

Short Title: PICqCPR
CPCCRN Protocol Number: 041

Lead Investigator and Author:
Robert Berg, M.D.
Children's Hospital of Philadelphia

Protocol Version: 1.03
Version Date: January 28, 2015

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: _____

THIS PAGE IS INTENTIONALLY BLANK.

Contents

1 Study Summary **7**
1.1 Hypotheses . . . 7
1.2 Specific Aims . . . 7
1.3 Subject Eligibility, Accrual and Study Duration . . . 8

2 Background and Significance **8**

3 Study Design **9**

4 Data Collection and Procedures **10**
4.1 Patient Characteristics . . . 10
4.2 CPR Event Characteristics . . . 11
4.3 Hemodynamic Variables . . . 12
4.4 Quality of CPR Data . . . 13
4.5 Pediatric Survival Outcome Data . . . 14

5 Data Analysis **14**
5.1 Sample Size . . . 17

6 Data Management **18**
6.1 Electronic Data Capture System . . . 18
6.2 Data Security . . . 19
6.3 Data Confidentiality . . . 19
6.4 Data Quality Management and Monitoring . . . 20
6.5 Record Access . . . 20

7 Protection of Human Subjects **21**

8 Health Insurance Portability and Accountability Act **22**

9 Inclusion of Women and Minorities **22**

10 Retention of Records **22**

Bibliography **23**

List of Tables

1 PICqCPR Pilot Data 17
2 Sample Size Estimates 18

1 Study Summary

1.1 Hypotheses

The hypotheses of this multicenter cohort study of in-hospital intensive care unit pediatric cardiac arrest in CPCCRN are:

1. Pediatric CPR events with average arterial diastolic blood pressures $\geq$ 30mmHg will be associated with a higher rate of ROSC.

2. Pediatric CPR events with average $ETCO_2 \geq$ 20mmHg will be associated with a higher rate of ROSC.

3. Arterial diastolic blood pressure and $ETCO_2$ during CPR, as surrogates of perfusion will be associated with survival outcomes.

4. Chest compression measurements (depth, rate, and fraction) during CPR will be associated with arterial diastolic blood pressure, $ETCO_2$, and survival outcomes.

The hypothesis concerning chest compression measurements will only be assessed at participating sites that are able to use a quality of CPR measurement device during CPR.

1.2 Specific Aims

This project includes the following Specific Aims:

Specific Aim 1. Assess the association between arterial diastolic blood pressures during CPR and the rate of ROSC $\geq$ 20 minutes.

Specific Aim 2. Assess the association between $ETCO_2$ during CPR and the rate of ROSC $\geq$20 minutes.

Specific Aim 3 (exploratory). Obtain evidentiary support associating arterial diastolic blood pressure and $ETCO_2$ measurements during CPR with survival outcomes.

Specific Aim 4 (Optional). Obtain evidence associating chest compression measurements (depth, rate, and fraction) during CPR with arterial diastolic blood pressure, $ETCO_2$, and survival outcomes.

Specific Aim 4 will only be carried out at participating sites that are able to use a quality of CPR measurement device during CPR.

1.3 Subject Eligibility, Accrual and Study Duration

Inclusion criteria: A CPR event will be eligible for study enrollment if the answer to both of the following questions is YES:

1. Did the patient receive chest compressions for ≥ 1 minute in the PICU or the CICU?
2. Is the patient ≥ 37 weeks gestational age and < 19 years of age?

A CPR event will be eligible for assessing quality of chest compression during CPR in participating institutions if a device (e.g., ZOLL R-series, Philips MRx, Physiocontrol LIFEPAK 20e) is FDA cleared for use according to the age of the patient.

Exclusion Criteria: A CPR event will be ineligible for study enrollment if the answer to any of the following questions is NO:

1. Did the patient have either an arterial line or $ETCO_2$ monitor in place at the time of chest compressions?
2. Were there useable waveform data available from either the arterial line or $ETCO_2$ monitor?
3. At the time the CPR Event began, was the patient free from ECMO therapy?

Based upon pilot CPCCRN data, approximately 260 CPR events are expected to occur on an annual basis, resulting in approximately 130 events with eligible arterial data (Please see Table 1: PICqCPR Pilot Data). We will plan a 3 year study with a targeted enrollment of 390 CPR Events.

2 Background and Significance

Cardiac arrests in children are a major public health problem. Thousands of children in the USA are treated in pediatric intensive care units (PICUs) with cardiopulmonary resuscitation (CPR) each year for sudden in-hospital cardiac arrest.[1–4] Neurological outcomes following these in-hospital PICU CPR events are often abnormal.[5–7] As children with neurological deficits following in-hospital CPR are a major burden for families and society, improving neurological outcomes through superior blood flow during CPR is an important clinical goal.

Studies in animals have established that survival following CPR for cardiac arrest depends on attaining adequate myocardial blood flow.[8, 9] Myocardial perfusion pressure, also known as coronary perfusion pressure (CPP) (determined mathematically as arterial diastolic pressure minus right atrial diastolic pressure) is the primary determinant of myocardial blood flow.[8, 9]

Limited adult data confirm the importance of attaining adequate coronary perfusion pressure for survival from CPR.[8, 10] However, there is a paucity of published hemodynamic data during CPR in children, so the relationship between hemodynamics during CPR and outcomes has not been rigorously evaluated in children and is a major knowledge gap.

Similarly, end-tidal carbon dioxide ($ETCO_2$) has also been used as a marker of CPR quality/intra-arrest hemodynamics (i.e., pulmonary blood flow).[11–14] Animal studies have established that $ETCO_2$ during CPR correlates with cardiac output and survival.[11, 12] Also, adult studies have confirmed that attaining adequate $ETCO_2$ is necessary for survival.[13, 14] Yet again, published pediatric data associating $ETCO_2$ during CPR with hemodynamics and survival outcomes is minimal. Currently the American Heart Association (AHA) recommends monitoring of $ETCO_2$ during pediatric CPR, using extrapolated data from animals and adults with little data collected from actual children.

Limited pediatric data describe the quality metrics of the delivery of CPR (e.g., depth of compression, rate, and fraction of chest compression) during in-hospital resuscitation,[15] nor the association of chest compression characteristics with hemodynamic and survival outcomes.[16–20]

Therefore, the objective of this investigation is to obtain evidentiary support to associate hemodynamics during CPR (arterial diastolic pressure and $ETCO_2$) with outcomes in those children who suffer an arrest within CPCCRN PICUs and CICUs. In addition, at participating sites that are able to use a quality of CPR device during CPR, measurements will be obtained to describe the characteristics of chest compressions (depth, rate, and fraction of compression) observed during CPR events.

3 Study Design

The overall objective of the Pediatric Intensive Care Quality of CPR (PICqCPR) Study is to measure high-fidelity hemodynamic data during CPR in CPCCRN intensive care units, and to evaluate the relationship between these parameters and important clinical outcomes.

The PICqCPR Study is a multicenter cohort study of in-hospital intensive care unit pediatric cardiac arrests within the CPCCRN network. The Pediatric Intensive Care Unit (PICU) and Cardiac Intensive Care Unit (CICU) are the only two locations within clinical centers that will be used for subject accrual.

For the purposes of this study, CPR is defined as administration of chest compressions for at least one minute. Return of circulation will be recorded, regardless of whether ECMO was utilized or not. The outcome metric for successful CPR is return of spontaneous circulation (ROSC) for at least 20 minutes duration. Repeat chest compression episodes for the same subject are eligible for inclusion. If a subject sustains ROSC for at least 20 minutes after chest compressions end, and then arrests again, it is considered a separate and new event.

4 Data Collection and Procedures

Note that the specific questions and choice sets that are 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 Scale (FSS)
- Was there an out-of-hospital cardiac arrest that led to this hospital admission?
- Date and time of hospital admission
- Date and time of ICU admission
- Location of event (PICU or CICU)
- Illness Category:
  - Medical cardiac
  - Medical non-cardiac
  - Surgical cardiac
  - Surgical non-cardiac
  - Trauma
- Pre-existing conditions (at time of CPR event):

- Respiratory insufficiency
- Hypotension
- Congestive heart failure
- Pneumonia
- Sepsis
- Trauma
- Renal Insufficiency
- Malignancy
- Congenital Heart Disease
  - If yes, single ventricle?
    - 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

4.2 CPR Event Characteristics

- Date and time of start of chest compressions
- Interventions in place at time of event:
  - Vascular Access
  - Arterial catheter
  - Central venous catheter
  - Vasoactive infusion
  - Invasive mechanical ventilation
  - $ETCO_2$ monitoring
  - Non-invasive ventilation
- Immediate cause of CPR Event:
  - Hypotension
  - Respiratory decompensation
  - Arrhythmia (VF, VT, SVT)
  - Cyanosis without respiratory decompensation
- Was it a witnessed CA?
- First documented rhythm requiring CPR:
  - VF
  - VT
  - Pulseless electrical activity [PEA]

  - Asystole
  - Bradycardia with pulses
- Open or closed sternum at onset of CPR event
- Date and time sternum opened during CPR event
- Time of first shockable rhythm
- Time of first attempted defibrillation for shockable rhythm
- Time of first administration of a vasopressor medication bolus
- Pharmacologic interventions during CPR:
  - Epinephrine
    - What was the total number of epinephrine doses?
  - Atropine
  - Calcium
  - Sodium Bicarbonate
  - Vasopressin
  - Amiodarone
  - Lidocaine
  - Fluid Bolus
  - Other (Specify)
- Date and time of end of chest compressions
- Outcome of CPR Event:
  - ROSC $\geq$ 20 minutes
  - Transition to ECMO with ROSC $<$ 20 minutes
  - Transition to ECMO without ROSC
  - Died

4.3 Hemodynamic Variables

The following variables will be collected once every minute for a maximum of ten minutes prior to the beginning of chest compressions:

- Heart rate
- Systolic arterial blood pressure
- Diastolic arterial blood pressure
- Mean arterial blood pressure
- $ETCO_2$
- Central venous pressure/Right atrial pressure
- Pulse oximetry SpO_2

Waveforms of the following variables will be provided throughout the duration of the first 10 minutes of chest compressions, as well as the last minute prior to the end of chest compressions.

- Arterial diastolic pressure
- Arterial systolic pressure
- Central venous pressure/Right atrial pressure
- $ETCO_2$
- Electrocardiogram (bedside monitor)
- Plethysmography (bedside monitor)
- Pulse oximetry SpO_2
- Actual chest compressions provided per minute

The following variables will be collected once every five minutes for the first 20 minutes after chest compressions have ended:

- Heart rate
- Systolic arterial blood pressure
- Diastolic arterial blood pressure
- Mean arterial blood pressure
- $ETCO_2$
- Central venous pressure/Right atrial pressure
- Pulse oximetry SpO_2

4.4 Quality of CPR Data

An optional component of this protocol involves obtaining quality of CPR data, including depth of chest compression, fraction of time during which compression occurs, and other digital data obtained from these devices. Data will be accepted from participating sites that have chest compression quality measurement capability (e.g., ZOLL R-series, Philips MRx, Physiocontrol LIFEPAK 20e).

- Is your site participating in the quality of CPR component of this study? (Yes/No)

If the answer to this question is yes, all digitally available chest compression data from the quality CPR device will be collected.

4.5 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 ICU discharge and hospital discharge
- FSS at ICU discharge and hospital discharge

5 Data Analysis

The first two specific aims of this study each involve demonstration of a significant association between ROSC and hemodynamic parameters. The most formal (and simplistic) hypothesis test will compare the proportions of patients in whom ROSC was achieved, among events with average arterial diastolic blood pressures $\geq$ 30mmHg versus $<$ 30mmHg (Aim 1) during CPR, and among events with average $ETCO_2 \geq 20$ mmHg versus < 20 mmHg during CPR (Aim 2).

The definition of "average" in the above statement is multiple, as variables such as average arterial BP will be available for one-minute epochs, for up to the first 10 minutes of CPR, as well as for the final minute of CPR, even if duration of CPR is over ten minutes. We shall define "average" in the following ways:

1. Average value during the first one-minute epoch of CPR
2. Average value during the last one-minute epoch of CPR, up to 10 minutes after CPR initiation
3. Average value during the last one-minute epoch of CPR, regardless of CPR duration
4. Average value over (up to) the first ten one-minute epochs of CPR

In addition, we will assess the proportion of total CPR time, during (up to) the first ten minutes of CPR, above which the parameters assessed are at or above, versus below, the arterial BP and $ETCO_2$ thresholds.

While the study aims will be assessed with respect to all of the above measures, we hypothesize *a priori* that values during the last one-minute period of CPR will be most strongly associated with ROSC. While this would seem to indicate use of definition "3."

above for the primary hypothesis test, it is possible that for events for which ROSC is not achieved despite lengthy CPR, CPR parameters during the final minute may reflect less aggressive efforts as futility of continued intervention becomes apparent. (Limited resources prevent collection of full data for arrests with longer duration of CPR, which is recognized as a limitation of this protocol.) Therefore, to avoid this potential bias, the primary hypothesis tests for Aims 1 and 2 will employ parameters during the final minute of CPR up to 10 minutes (definition "2.") above.

While analyses using other variants of hemodynamic parameters will also be explored, the definition "4." above will be of particular interest as it is unknown whether achieving, versus maintaining, a particular pressure is more important for achieving a favorable outcome. Exploratory analyses will assess which definition is a more powerful predictor of ROSC, overall and stratified by duration of CPR. Since all of these parameter definitions are related and findings are expected to be highly consistent between the different definitions, no adjustment for multiple comparisons will be made in these exploratory analyses, which will be clearly denoted as such. Reporting of results will describe all definitions considered and findings from these investigations.

For Specific Aim 3, 24-hours survival, survival to hospital discharge, and survival with favorable neurologic outcome are the survival outcomes that will be examined. While again various hemodynamic parameter summaries will be considered, we hypothesize *a priori* that proportion of time that CPR is above acceptable arterial DBP and $ETCO_2$ thresholds is most strongly associated with the various survival outcomes. The primary analysis will assess the relationship between survival at hospital discharge with proportion of time hemodynamic parameters are at or above the thresholds described for Aims 1 and 2.

Significance of association will be assessed by approaches that take into account the possibility for multiple events during the same hospitalization for the same patient. While rates of ROSC will be reported on a per-event basis, the primary comparison of ROSC rates between subgroups of events will be performed incorporating within-patient correlation. While this is possible to carry out using several approaches, we propose using generalized estimating equations (GEE) within a modified Poisson regression model,[21] as estimation of relative risk and adjustment for other factors is facilitated with this approach (as discussed below). Magnitude of association between the dichotomized parameter levels and outcome will be quantified by calculating relative risk of ROSC, along with 95% confidence interval, for children whose hemodynamic parameter is favorable (e.g., DBP $\geq$ 30mmHg) versus others.

As this study is considered exploratory in nature, a two-sided test with Type I error of 0.05 will be performed separately for each of the two hemodynamic parameters, and again separately for the Aim 3 evaluations.

Beyond this basic analysis, we will examine alternative cut points for the two hemodynamic parameters as predictors of ROSC, and more generally assess their overall association with ROSC, via the use of receiver operating characteristic curves. This approach may determine alternative hemodynamic parameter cut points strongly associated with ROSC; utility of criteria determined in this fashion will require validation in future studies.

It will also be important to determine the association of hemodynamic parameters with outcomes, adjusted for patient risk profile and event characteristics up until the time of arrest. For binary outcomes such as ROSC and survival, multivariable regression models will be used to assess this association. As ROSC and other favorable outcomes are not expected to be rare events, we will analyze this prospective study by estimating the relative risk of an event rather than the odds ratio, using the modified Poisson regression approach.[21] As the number of potential adjustment variables is large relative to the number of events, factors for adjustment will be selected from those showing relatively strong statistical association with each outcome. Specific modeling strategies will be documented in more detail in the Statistical Analysis Plan.

While we will compare absolute values of PCPC and FSS between patient subgroups defined by hemodynamic and other parameters, we also expect to dichotomize these outcome measures for similar analyses. An exploratory outcome measure of interest will be "survival with favorable outcome," which may be defined as discharge alive without substantial worsening of PCPC/FSS relative to pre-event status and discharge alive with PCPC 1-3.

For Specific Aim 4, we will describe the quality of chest compression measurements (compression depth, rate, and fraction of time compressed) during CPR, and measure association with arterial diastolic blood pressure, $ETCO_2$, and survival outcomes.

This project will have no formal interim analyses scheduled. It is recognized that accumulating data from this study may be analyzed, for example at annual study updates, for presentation at scientific meetings or to assess magnitude of treatment effects for trial planning, prior to study completion. Care will be taken to ensure that such preliminary analyses do not influence study accrual goals.

5.1 Sample Size

Based upon pilot CPCCRN data, approximately 260 CPR events are expected to occur on an annual basis, resulting in approximately 130 events with eligible arterial data (See Table 1: PICqCPR Pilot Data).

Table 1: PICqCPR Pilot Data

Site:	**#wks:**	**#CPR events:**	**Arterial Catheter at time of CPR:**	**Eligible Arterial Catheter Data:**	**Annual Eligible CPR Events with Arterial Catheter Data:**
CHOM	20	13	7(54%)	5(38%)	13
CHOP	20	9	3(33%)	3(33%)	7
CNMC	17.1	21	14(67%)	11(52%)	33
CHLA	19.3	16	8(50%)	8(50%)	21
UCLA	20	9	7(78%)	5(56%)	13
MICH	18	10	7(70%)	6(60%)	17
PHNX	20	11	6(55%)	6(55%)	15
UPMC	20	8	6(75%)	5(63%)	13
Totals:	**n/a**	**97**	**58(60%)**	**49(51%)**	**132**

Further, based upon CHOP limited preliminary data, we can assume that approximately 60% of pediatric CPR events will have average event arterial diastolic blood pressures exceeding 30 mmHg. We must also assume that 30% of events with average arterial diastolic blood pressures less than 30 mmHg will still obtain ROSC, based upon large registry data.[22] Using these conservative estimates, in just one year, we will have

more than 90% power to detect a doubling in likelihood of ROSC (∼60% ROSC rate) when the event average diastolic pressure exceeds 30 mmHg. However, in light of the higher number of subjects needed to determine if the ROSC rate associated with higher arterial diastolic pressures would be 50% more (a very important clinical effect), 3-4 years may be necessary for more than 80% power to detect a significant effect in the setting of a 50% increase. Because this will be the first study to assess the association of CPR hemodynamics with outcomes in children, we will plan a 3 year study with 390 CPR events.

For additional examples of estimated sample sizes needed for substantial power when these parameters are varied, see Table 2: Sample Size Estimates. (These estimates are approximate, as correlation between multiple events occurring in the same patient may slightly affect power).We do not expect this study to have high power for detecting a significant association between hemodynamic parameters and survival, as effect on patient survival outcomes is expected to be substantially moderated relative to beneficial effect on acute ROSC.

Table 2: Sample Size Estimates

DBP ≥ 30mmHg:	**ROSC Rate if DBP ≥ 30mmHg:**	**50% Effect; N=80%, 90% power:**	**100% Effect; N=80%, 90% power:**	**150% Effect; N=80%, 90% power:**
50%	30%	n=352, 460	n=96, 122	n=46, 58
60%	30%	n=368, 483	n=103, 130	n=46, 60
70%	30%	n=424, 550	n=117, 150	n=50, 67

6 Data Management

6.1 Electronic Data Capture System

In this study, de-identified waveform data will be provided to the expert reviewers via a secure electronic website which is maintained at the Data Coordinating Center (DCC). All research coordinators and investigators will be trained through an in-person and/or

web-based training session before the start of the project, and topics will include data abstraction, collection, study workflow, and the data entry process.

6.2 Data Security

The DCC is located at the University of Utah in Salt Lake City, Utah. The DCC has a state-of-the-art computer infrastructure with a dedicated server room with a fire suppression system, air conditioning, and separate air filtering. The server facility is locked separately from the remainder of the DCC and access to the building is monitored by security personnel year round. The DCC coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the DCC with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes three high speed switches and two hubs. 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. The electronic data capture system (EDC) (Web-based collaborative workspace), and other web applications use the SSL protocol to transmit data securely over the Internet. Direct access to DCC machines is only available while physically located inside the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against DCC servers, and DCC IT staff are notified of intrusion alerts.

Servers are backed up daily through a dedicated backup server and internal high speed network. Incremental backups occur hourly and nightly. Full system backups occur nightly and weekly with off-site rotations. 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 6 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.

6.3 Data Confidentiality

The investigators and staff of the DCC are fully committed to the security and confidentiality of all data collected for CPCCRN studies. All DCC personnel at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at

the University of Utah. In addition, all personnel involved with DCC data systems have received Human Subjects Protection and Health Insurance Portability and Accountability Act (HIPAA) education.

The coordinators, reviewers, and investigators involved with this study will be required to sign agreements from the DCC that relate to maintenance of passwords, information system security, and data confidentiality.

6.4 Data Quality Management and Monitoring

The DCC monitors CPCCRN studies on behalf of the investigators and the funding agency. The purposes of monitoring include demonstration of adherence to human subjects protection requirements and assurance of high quality study data. Monitoring is done remotely and may also involve physical site monitoring visits.

Remote monitoring: The DCC will supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the clinical center and telephone consultations with the clinical center investigator and/or research coordinator to review data quality. This requires uploading de-identified copies of specific parts of the medical record to the DCC staff, who review those materials against the data recorded in the electronic data capture system.

Site monitoring visits: Site monitoring visits may be conducted during the study to review patient entry, data quality, and to assure regulatory compliance. The site monitoring visits would include an on-site meeting of the monitor, the clinical center investigator, and his/her staff. The primary purpose of site monitor visits is to review compliance with the study methodology and adherence to Good Clinical Practice guidelines. The site monitor will provide each site with a written report and sites will be required to follow up on any deficiencies.

6.5 Record Access

The medical record must be made available to authorized representatives of the DCC 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 of the National Institutes of Health, and the Institutional Review Board (IRB) for each study site, if appropriate.

7 Protection of Human Subjects

Institutional Review Board (IRB) Approval: The DCC and each Clinical Center must obtain approval from their respective IRB prior to participating in the study. This may also be accomplished via a Central IRB mechanism within the network. The DCC will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

Potential Risks and Benefits: There are no physical risks associated with participating in this study, as this is an observational study and no therapeutic intervention is being tested. There is a minor risk of loss of confidentiality. This is mitigated by data security procedures at the DCC. There is no immediate direct benefit to subjects enrolled in this study. The potential benefit to future patients is that more effective strategies for CPR may be developed to improve the survival rate and reduce morbidity from CPR in children.

For sites participating in chest compression quality measurements, this may be done with existing equipment in their institution, or with a ZOLL R-series defibrillator provided by the study. If the site uses a device provided by the study, then it is the site's responsibility to assure training on the use of the device in the intensive care unit. These devices are in use in many children's hospitals; the potential incremental risk relates to having an unfamiliar piece of equipment to be used during CPR. This risk is mitigated by proper training concerning the device. It is recognized that some institutions may not permit a different defibrillator to be used in their setting, and for this reason, participation in this portion of the protocol is optional, and participation is determined on a site by site basis.

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.

Informed Consent: Waiver of consent is requested for observational data collection for each patient eligible for this study. The justification for waiver of consent for observational data collection 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 and no changes in clinical practice.
3. The minimal risk of loss of privacy is mitigated by secure data management at the DCC, and analysis datasets will be de-identified.

Adverse Events: Adverse events will not be collected in this observational, non-interventional study.

8 Health Insurance Portability and Accountability Act

The abstracted data will be de-identified with respect to patient identifiers. Dates will be recoded after entry into the EDC, and the DCC will create a completely de-identified analytical database for use by the study investigators, and for final archiving. All study sites have been or will be offered Business Associate Agreements (BAA) with the University of Utah. Copies of signed BAA are maintained at the DCC.

9 Inclusion of Women and Minorities

The gender, ethnic and racial composition of patients enrolled in all CPCCRN studies is a function of the underlying referral population at each Clinical Center selected by the National Institute of Child Health and Human Development (NICHD) to participate in the network. There will be no exclusion of patients based on gender, race, or ethnicity.

10 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)].

Bibliography

[1] Parra DA, Totapally BR, Zahn E, Jacobs J, Aldousany A, Burke RP, et al. Outcome of cardiopulmonary resuscitation in a pediatric cardiac intensive care unit. Crit Care Med. 2000 Sep;28(9):3296–3300.

[2] Peddy SB, Hazinski MF, Laussen PC, Thiagarajan RR, Hoffman GM, Nadkarni V, et al. Cardiopulmonary resuscitation: special considerations for infants and children with cardiac disease. Cardiol Young. 2007 Sep;17 Suppl 2:116–126. Available from: http://dx.doi.org/10.1017/S1047951107001229.

[3] Randolph AG, Gonzales CA, Cortellini L, Yeh TS. Growth of pediatric intensive care units in the United States from 1995 to 2001. J Pediatr. 2004 Jun;144(6):792–798. Available from: http://dx.doi.org/10.1016/j.jpeds.2004.03.019.

[4] Slonim AD, Patel KM, Ruttimann UE, Pollack MM. Cardiopulmonary resuscitation in pediatric intensive care units. Crit Care Med. 1997 Dec;25(12):1951–1955.

[5] 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 Jan;295(1):50–57.

[6] Meert KL, Donaldson A, Nadkarni V, Tieves KS, Schleien CL, Brilli RJ, et al. Multicenter cohort study of in-hospital pediatric cardiac arrest. Pediatr Crit Care Med. 2009 Sep;10(5):544–553. Available from: http://dx.doi.org/10.1097/PCC.0b013e3181a7045c.

[7] Meaney PA, Nadkarni VM, Cook EF, Testa M, Helfaer M, Kaye W, et al. Higher survival rates among younger patients after pediatric intensive care unit cardiac arrests. Pediatrics. 2006 Dec;118(6):2424–2433.

[8] Berg RA, Hemphill R, Abella BS, Aufderheide TP, Cave DM, Hazinski MF, et al. Part 5: adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010 Nov;122(18 Suppl 3):S685–S705. Available from: http://dx.doi.org/10.1161/CIRCULATIONAHA.110.970939.

[9] Berg RA, Kern KB, Hilwig RW, Ewy GA. Assisted ventilation during 'bystander' CPR in a swine acute myocardial infarction model does not improve outcome. Circulation. 1997 Dec;96(12):4364–4371.

[10] Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA. 1990 Feb;263(8):1106–1113.

[11] Kern KB, Sanders AB, Voorhees WD, Babbs CF, Tacker WA, Ewy GA. Changes in expired end-tidal carbon dioxide during cardiopulmonary resuscitation in dogs: a prognostic guide for resuscitation efforts. J Am Coll Cardiol. 1989 Apr;13(5):1184–1189.

[12] Ornato JP, Garnett AR, Glauser FL. Relationship between cardiac output and the end-tidal carbon dioxide tension. Ann Emerg Med. 1990 Oct;19(10):1104–1106.

[13] Sanders AB, Kern KB, Otto CW, Milander MM, Ewy GA. End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. A prognostic indicator for survival. JAMA. 1989 Sep;262(10):1347–1351.

[14] Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. N Engl J Med. 1997 Jul;337(5):301–306. Available from: http://dx.doi.org/10.1056/NEJM199707313370503.

[15] Meaney PA, Bobrow BJ, Mancini ME, Christenson J, de Caen AR, Bhanji F, et al. Cardiopulmonary resuscitation quality: [corrected] improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. Circulation. 2013 Jul;128(4):417–35.

[16] Sutton RM, French B, Niles DE, Donoghue A, Topjian AA, Nishisaki A, et al. 2010 American Heart Association recommended compression depths during pediatric in-hospital resuscitations are associated with survival. Resuscitation. 2014 Sep;85(9):1179–84.

[17] Sutton RM, French B, Nishisaki A, Niles DE, Maltese MR, Boyle L, et al. American Heart Association cardiopulmonary resuscitation quality targets are associated with improved arterial blood pressure during pediatric cardiac arrest. Resuscitation. 2013 Feb;84(2):168–72.

[18] Sutton RM, Niles D, French B, Maltese MR, Leffelman J, Eilevstjønn J, et al. First quantitative analysis of cardiopulmonary resuscitation quality during in-hospital cardiac arrests of young children. Resuscitation. 2014 Jan;85(1):70–4.

[19] 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 Jul;42(7):1688–95.

[20] Sutton RM, Wolfe H, Nishisaki A, Leffelman J, Niles D, Meaney PA, et al. Pushing harder, pushing faster, minimizing interruptions... but falling short of 2010 cardiopulmonary resuscitation targets during in-hospital pediatric and adolescent resuscitation. Resuscitation. 2013 Dec;84(12):1680–4.

[21] Donoghue A, Berg RA, Hazinski MF, Praestgaard AH, Roberts K, Nadkarni VM, et al. Cardiopulmonary resuscitation for bradycardia with poor perfusion versus pulseless cardiac arrest. Pediatrics. 2009 Dec;124(6):1541–1548.

[22] Greenland S. Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. Am J Epidemiol. 2004 Aug;160(4):301–305. Available from: http://dx.doi.org/10.1093/aje/kwh221.