

**Improving Outcomes from Pediatric Cardiac
Arrest
Manual of Operations
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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The protocol described in this Manual of Operations is CPCCRN Protocol Number 068, and the lead CPCCRN investigators for this protocol are Robert M. Sutton, M.D., M.S.C.E., Children's Hospital of Philadelphia.

Contents

I	The Network and Protocol	1
1	Introduction	3
1.1	CPCCRN Background	3
1.2	Purpose of Manual	4
1.3	Role of DCC	4
1.4	Annual IRB Approval	5
1.5	Central IRB Review	6
2	Study Protocol	7
2.1	Study Summary	9
2.1.1	Hypotheses	9
2.1.2	Specific Aims	9
2.1.3	Subject Eligibility, Accrual and Study Duration	10
2.2	Rationale and Background	10
2.3	Study Design and Intervention	12
2.3.1	Study Design Overview	12
2.3.2	Description of the Bundle	12
2.3.3	Compliance with the Intervention	15
2.4	Data Collection	15
2.4.1	Patient Characteristics	15
2.4.2	CPR Event Characteristics	18
2.4.3	Hemodynamic Variables	20
2.4.4	CPR Quality Variables	20
2.4.5	Post-CPR Care Variables	20
2.4.6	Pediatric Survival Outcome Data	21
2.4.7	Point of Care Training Data	22
2.5	Data Analysis	22
2.5.1	Specific Aim Analyses	22

2.5.2	Sample Size Calculations and Statistical Power	23
2.6	Data Management	23
2.6.1	Electronic Data Capture System	24
2.6.2	Study Monitoring	24
2.6.3	Data Coordinating Center	25
2.6.4	Record Access	28
2.7	Protection of Human Subjects	29
2.7.1	Institutional Review Board (IRB) Approval	29
2.7.2	Potential Risks and Benefits	29
2.7.3	Protection Against Risks	29
2.7.4	Informed Consent	30
2.8	Data and Safety Monitoring Plan	30
2.8.1	Data Safety Monitoring Board (DSMB)	30
2.8.2	Adverse Event Reporting	31
2.9	Study Training	31
2.10	Regulatory Issues	32
2.10.1	Health Insurance Portability and Accountability Act	32
2.10.2	Inclusion of Women and Minorities	32
2.10.3	ClinicalTrials.gov Requirements	32
2.10.4	Retention of Records	32
2.10.5	Public Use Data Set	33
II	Good Clinical Practice	41
3	Good Clinical Practice (GCP)	43
3.1	CPCCRN Data Coordinating Center Policy	43
3.2	Project Site Monitoring	44
3.3	Essential Documents Binder	45
3.4	Archiving Study Records	46
3.5	IRB - Investigator Interactions	46
3.6	Clinical Center Site Inspections	47
3.7	Audits	48
4	Data Safety Monitoring Board	51

5	Site Monitoring Visits	53
5.1	Monitoring by DCC	53
5.1.1	Site Monitoring Visits	53
5.1.2	Document Review During Site Monitoring Visits	54
5.1.3	Remote Monitoring	56
6	Institutional Review Board	61
6.1	Documentation of IRB Review	61
6.2	What If IRB Approval Is Denied?	62
6.3	Review Date Clarification	63
6.4	Consequences of Tardy Annual Review	64
6.5	Local IRB Amendments	64
7	Investigator Responsibility	65
7.1	Investigator Qualifications and Agreements	65
7.2	Communication with IRB	66
7.3	Compliance with Study Protocol	67
7.4	Protocol Amendments	67
7.5	Premature Study Termination	68
7.5.1	By Principal Investigator	68
7.5.2	By Clinical Center's IRB	68
8	Staff Responsibilities	69
8.1	Staff Training	69
8.2	Screen Locations for Eligible Patients	70
8.3	IRB Approval	70
8.4	Maintain Essential Documents Binder	70
8.5	Document Responsibilities	70
8.6	Study Specific Staff Responsibilities	71
III	Study Management	73
9	Study Workflow	75
9.1	Preparation	76
9.2	Definition of a CPR Event	77
9.3	Screening	77
9.4	Eligibility	78

9.5	Waiver of Consent	79
9.6	Transition & Implementation of Bundle	79
9.7	Data Collection	80
9.7.1	CPR Event Waveform Data	80
9.7.2	CPR Event Characteristics	81
9.7.3	<i>ETCO₂</i> Waveform Information	89
9.7.4	Post-CPR Event Hemodynamic Variables	89
9.7.5	PRISM & Glasgow Coma Scale	90
9.7.6	Demographics	91
9.7.7	Baseline FSS and PCPC	91
9.7.8	Hospitalization Information	92
9.7.9	Discharge FSS and PCPC	93
9.7.10	Death Data	93
9.7.11	ICU Information	93
9.8	Adverse Events	95
9.9	Additional Study Resources	95
9.9.1	Functional Status Scale	95
9.9.2	Pediatric Cerebral Performance Category	105
10	Data Management	107
10.1	Data Entry Contact for Questions	108
10.2	Global Data Entry	108
10.3	Study Events and Electronic Case Report Forms	109
10.4	eCRF Specific Data Entry Guidelines	111
10.4.1	Eligibility	111
10.4.2	CPR Event Characteristics	111
10.4.3	Post-CPR Event Care Variables	111
10.4.4	PRISM	112
10.4.5	Vasoactive Inotropic Score	112
10.4.6	Waveform and Defibrillation Data Upload Information	112
10.4.7	CPR Later Found to be Unnecessary	112
10.4.8	<i>ETCO₂</i> Waveform Information	113
10.4.9	Demographics and Physical Measurements	113
10.4.10	Baseline Functional Assessments	113
10.4.11	Hospitalization Summary	113
10.4.12	ICU Dates and Other Information	113
10.5	Survey Data Entry	113

IV	Appendices	115
A	Use of eRoomTM in CPCCRN	117
A.1	How to Connect	118
A.2	CPCCRN Steering Committee eRoom	119
A.3	Common Items	122
A.3.1	Folders and Files	122
A.3.2	Web Links	122
A.3.3	Polls	124
A.3.4	Databases	124
A.4	How to Use Versioning	126
A.5	eRoom TM Backup	127
B	Use of OpenClinica 3.1 Electronic Data Capture Software	129
B.1	What is OpenClinica?	130
B.2	Accessing OpenClinica Studies	130
B.3	Subjects and Events	132
B.4	Adding a New Subject	133
B.5	Scheduling an Event	133
B.6	Selecting and Entering Specific eCRFs	135
B.7	Viewing or Printing eCRFs	135
B.8	Entering Data in eCRFs	138
B.8.1	eCRF Header	138
B.8.2	Main Body of the eCRF	138
B.9	Discrepancy Alerts	140
B.10	Adding Rows to a Repeating Question Group	141
B.11	Uploads	142
B.12	Deletion of Study Subject IDs, Study Events and eCRFs	142
B.13	Getting Help	142
B.14	How to Log Out	143
B.15	What If the Internet Is Down?	143
	Index	145

List of Tables

8.1 Delegated Responsibilities Worksheet 72

List of Figures

2.1	Schematic summary of overall study design	13
2.2	Point of care bedside refresher training.	14
5.1	Site Monitoring Sample Letter	58
5.2	Remote Monitoring Sample Letter	59
9.1	Functional Status Scale	96
9.2	Pediatric Cerebral Performance Category	106
A.1	Logging in to eRoom TM	118
A.2	Changing your password.	119
A.3	Password Recovery	120
A.4	Active eRoom Listing	120
A.5	Busy User Screen	121
A.6	Steering Committee eRoom	123
A.7	Pertussis Folder Example	124
A.8	Showing contact information by name.	125
A.9	Showing contact information by organization.	125
A.10	Showing contact information by role in network.	126
A.11	Right clicking the mouse to turn on version tracking.	127
B.1	Logging into OpenClinica	131
B.2	Homepage navigation screen	132
B.3	“Add Subject” screen	134
B.4	“Schedule Study Event for (Study Subject ID)” screen	136
B.5	“Enter or Validate Data for eCRFs in (Event Name)”	137
B.6	Anatomy of OpenClinica	139
B.7	Discrepancy Alerts	141

Part I

The Network and Protocol

Chapter 1

Introduction

Contents

1.1	CPCCRN Background	3
1.2	Purpose of Manual	4
1.3	Role of DCC	4
1.4	Annual IRB Approval	5
1.5	Central IRB Review	6

1.1 CPCCRN Background

The NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN) consists of a team of academic Clinical Centers and a Data Coordinating Center, as well as the National Institute of Child Health and Human Development. The seven Clinical Centers have agreed to investigate problems in clinical pediatric critical illness and injury in a collaborative manner. Each Center brings different research strengths to the Network. The Data Coordinating Center was selected on the basis of experience with the coordination of multi-center clinical trials, and proven expertise in study design, data management and biostatistical analysis. The CPCCRN data coordinating center (DCC) is located at the University of Utah.

1.2 Purpose of the Manual of Operations

After a CPCCRN study is approved for implementation by the Steering Committee, and the protocol is fully developed by the study Principal Investigator and the protocol subcommittee, the DCC will prepare a Manual of Operations (MOO). The MOO is to be used by the Principal Investigator (PI), Co-Investigators, Research Coordinators and data collectors at each participating Clinical Center to ensure that the study procedures are followed as uniformly as possible. The MOO includes details regarding patient eligibility and recruitment, informed consent, regulatory issues, data collection and flow, data entry, and procedures for reporting adverse medical events (when applicable). The MOO is produced as an operational, thorough, and adequately detailed document to be used as a reference by all Clinical Center personnel associated with a CPCCRN study. The MOO is distinct from the study protocol that has been approved by the CPCCRN for implementation. The MOO is much more detailed, and attempts to bridge the gap between designing the protocol and actually implementing the study. If the MOO and the study protocol are not in agreement, which will only occur in the event of error, the study protocol remains the definitive document. If readers of the MOO identify discrepancies between this MOO and the underlying study, they should contact the DCC so that the error may be fixed.

1.3 Role of Data Coordinating Center (DCC)

The Data Coordinating Center (DCC) is responsible for assisting CPCCRN investigators in the design and development of protocols, data management, providing biostatistical expertise and analysis of study data, and assistance with publication of research findings. In addition, the DCC is responsible to facilitate the logistics of study implementation. DCC staff work with the study PI, the study protocol subcommittee, the Steering Committee, the National Institute for Child Health and Human Development (NICHD) and the National Heart, Lung, and Blood Institute (NHLBI) staff throughout all phases of the research: planning, protocol development, peer review, patient recruitment, data collection, data management, data analyses, and publication.

1.4 Annual Institutional Review Board (IRB) Approval

It is required by law that all studies involving human subjects be reviewed at least annually by the Institutional Review Board (IRB) at each Clinical Center. Reviews may be conducted more frequently than yearly at the discretion of the local IRB. It is the responsibility of the Clinical Center investigator and the local IRB to ensure that these yearly reviews occur.

For CPCCRN studies, the DCC staff will attempt to remind the investigators and research coordinators at each Clinical Center to renew their IRB application for the study, two to three months in advance of the anticipated deadline. Upon request, the DCC will also provide the investigators with material that may be requested by the Clinical Center IRB, such as a summary of adverse events or summarized patient accrual information. The IRB will not be provided with blinded outcome data, but for blinded studies, approval of the Data Safety Monitoring Board (DSMB) will be provided in writing for submission to the Clinical Center IRB.

The DCC must have a copy of the local IRB approval and renewal notices in order for a Clinical Center to participate in a CPCCRN study. The approval letter must be on institutional letterhead and include a statement expressing that the yearly review has taken place, the date of the review, the expiration of the approval, and the outcome of the review. It is imperative that this letter indicate the *version* of the protocol that has been approved. This is critical because most study protocols undergo periodic revision, and IRB approval notices need to document that the approval refers to the most current version of the study protocol.

The University of Utah IRB does not permit the DCC to accept data from a CPCCRN Clinical Center unless the DCC has documentation of local IRB approval, as described in the previous paragraphs. Data submission will be suspended until such documentation is submitted to the DCC.

To reiterate a crucial point, the DCC will make good faith efforts to remind CPCCRN investigators of their annual IRB review. However, the ultimate responsibility to ensure annual review rests with the Clinical Center investigator and the local clinical site IRB. There is no guarantee of DCC reminders, and failure to maintain local IRB approval will result in suspension from study participation in all instances.

1.5 Central IRB Review

A Central Institutional Review Board (CIRB) has been instituted for this study at the University of Utah. Each Clinical Center that agrees to rely on the University of Utah IRB for review and continuing oversight of its human subjects research for the Improving Outcomes from Pediatric Cardiac Arrest study will need to sign a Reliance Agreement. The agreement allows the University of Utah to act as the IRB of record for the participating Collaborative Pediatric Critical Care Research Network Clinical Center.

Chapter 2

Study Protocol

Contents

2.1	Study Summary	9
2.1.1	Hypotheses	9
2.1.2	Specific Aims	9
2.1.3	Subject Eligibility, Accrual and Study Duration	10
2.2	Rationale and Background	10
2.3	Study Design and Intervention	12
2.3.1	Study Design Overview	12
2.3.2	Description of the Bundle	12
2.3.3	Compliance with the Intervention	15
2.4	Data Collection	15
2.4.1	Patient Characteristics	15
2.4.2	CPR Event Characteristics	18
2.4.3	Hemodynamic Variables	20
2.4.4	CPR Quality Variables	20
2.4.5	Post-CPR Care Variables	20
2.4.6	Pediatric Survival Outcome Data	21
2.4.7	Point of Care Training Data	22
2.5	Data Analysis	22
2.5.1	Specific Aim Analyses	22

2.5.2	Sample Size Calculations and Statistical Power . . .	23
2.6	Data Management	23
2.6.1	Electronic Data Capture System	24
2.6.2	Study Monitoring	24
2.6.3	Data Coordinating Center	25
2.6.4	Record Access	28
2.7	Protection of Human Subjects	29
2.7.1	Institutional Review Board (IRB) Approval	29
2.7.2	Potential Risks and Benefits	29
2.7.3	Protection Against Risks	29
2.7.4	Informed Consent	30
2.8	Data and Safety Monitoring Plan	30
2.8.1	Data Safety Monitoring Board (DSMB)	30
2.8.2	Adverse Event Reporting	31
2.9	Study Training	31
2.10	Regulatory Issues	32
2.10.1	Health Insurance Portability and Accountability Act	32
2.10.2	Inclusion of Women and Minorities	32
2.10.3	ClinicalTrials.gov Requirements	32
2.10.4	Retention of Records	32
2.10.5	Public Use Data Set	33

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).

2.1 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.

2.1.1 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.

2.1.2 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.

2.1.3 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.

2.2 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).

2.3 Study Design and Intervention

2.3.1 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 2.1 summarizes the overall study design.

2.3.2 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 2.2 on page 14). 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:

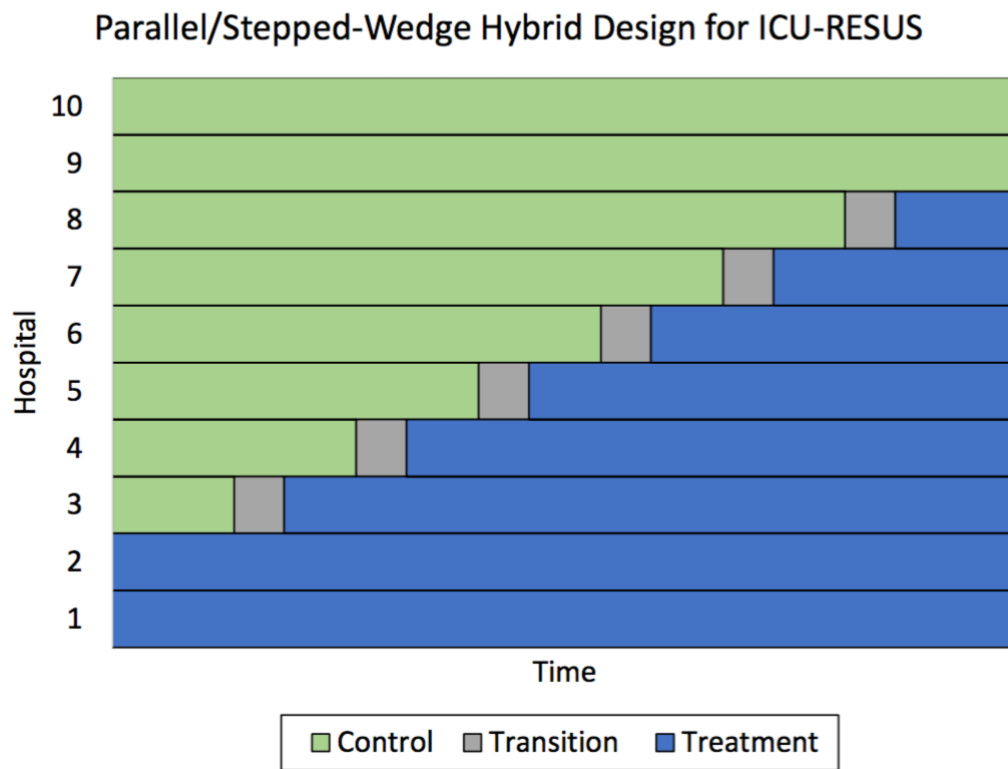


Figure 2.1: Schematic summary of overall study design



Figure 2.2: Point of care bedside refresher training.

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

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.

2.3.3 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.

2.4 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.

2.4.1 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) (10³/microliter)
- Lowest platelet count (10³/microliter)
- Highest PT (seconds)
- Highest PTT (seconds)

2.4.2 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)
 - ETCO₂ 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

2.4.3 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)

2.4.4 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])

2.4.5 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 PaO₂ (mmHg)
- PCO₂ (mmHg)

- pH
- Highest lactate (mmol/L)
- Glucose (mg/dL)
- Pulse oximetry (SpO₂)
- Required ECMO support for entire 24 hours (Y/N)

- Targeted temperature management (Y/N)
 - Goal max temperature:
 - * 32° - 34°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)

2.4.6 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

2.4.7 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.

2.5 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.

2.5.1 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.

2.5.2 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.

2.6 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.

2.6.1 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.

2.6.2 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.

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.

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.

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.

2.6.3 Data Coordinating Center

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.

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.

2.6.4 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.

2.7 Protection of Human Subjects

2.7.1 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.

2.7.2 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.

2.7.3 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.

2.7.4 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.

2.8 Data and Safety Monitoring Plan

2.8.1 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.

2.8.2 Adverse Event Reporting

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

2.9 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.

2.10 Regulatory Issues

2.10.1 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.

2.10.2 Inclusion of Women and Minorities

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

2.10.3 ClinicalTrials.gov Requirements

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

2.10.4 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)].

2.10.5 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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Part II

Good Clinical Practice

Chapter 3

Good Clinical Practice (GCP)

Contents

3.1	CPCCRN Data Coordinating Center Policy . .	43
3.2	Project Site Monitoring	44
3.3	Essential Documents Binder	45
3.4	Archiving Study Records	46
3.5	IRB - Investigator Interactions	46
3.6	Clinical Center Site Inspections	47
3.7	Audits	48

3.1 CPCCRN Data Coordinating Center Policy

The CPCCRN Data Coordinating Center (DCC) at the University of Utah School of Medicine has a policy that all CPCCRN studies will be conducted in compliance with Good Clinical Practices (GCP).¹ Good clinical practice

¹ Good Clinical Practice (GCP) was prepared by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1997) and published by the US Food and Drug Administration (FDA) on May 9, 1997 (see 62 FR 25691). GCP was published with the objective of providing a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

(GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The intent of this policy is to safeguard human subjects' welfare, assure validity of research data, and help assure that the CPCCRN will remain, as a whole, in compliance with regulatory requirements.

The DCC will:

- present educational information about GCP to investigators and research coordinators at CPCCRN Steering Committee meetings and specific study training sessions;
- provide manuals and materials to assist each Clinical Center in organizing essential documents and records;
- advise and assist each Clinical Center in understanding and meeting GCP requirements throughout all CPCCRN studies;
- organize site monitoring visits to each Clinical Center, as appropriate to the specific study, in coordination and with approval from National Heart,Lung, and Blood Institute (NHLBI);
- and serve as a central point of review and distribution of site monitoring visit reports.

Personnel at a Clinical Center may contact the DCC Principal Investigator, Program Director or Project Manager with any questions concerning this material. Contact information is available in the *eRoomTM* facility.

3.2 Project Site Monitoring

In some multi-institutional studies, the DCC assigns a site monitor to travel to each Clinical Center at times appropriate to the specific study. Site monitoring visits are often conducted at site initiation, during a study, and at close out of the study. Site monitoring for CPCCRN studies will be planned

in accordance with the technical requirements and difficulty of the study, with approval by the NHLBI.

It is anticipated that site monitoring will be required for the ICU-RESUS. For more information regarding site monitoring specific to this study, please refer to [Chapter 5 on page 53](#). Certain documents should be available at the Clinical Center so that at any time, these could be presented to an authorized visitor:

- Original study protocol
- Current study protocol
- Essential Documents Binder - maintained and current
- Institutional Review Board (IRB) submission packet and approval
- Protocol amendments and IRB amendment approvals
- Current IRB Approval

In order for a Clinical Center to participate in any study, the DCC must have a copy of the IRB approval from that site. The DCC at the University of Utah is prohibited (by the University of Utah IRB) from accepting data submission from a Clinical Center if this requirement is not met. More information concerning IRB approval is included later in this chapter (on the following page) and in [Chapter 6 on page 61](#).

3.3 Essential Documents Binder

The Essential Documents Binder consists of regulatory records and materials at the participating Clinical Center pertaining to the study. This includes regulatory documents, IRB correspondence, and other documents listed in the previous section. In addition, subject files (both case report forms and supporting medical records) are referenced from this binder. This means that the binder should indicate where the subject records are maintained.

These documents comprise the investigator's portion of what GCP terms Essential Documents for the conduct of a clinical trial. When combined with the sponsor's documentation, these documents are used by Federal agencies to permit evaluation of the conduct of the trial and the quality of the data produced.

For the purposes of organizing the Essential Documents, the DCC adopts the approach most commonly used, and recommends maintaining Essential Documents in a physical binder called the “Essential Documents Binder”. Each Clinical Center will be provided an empty Essential Documents Binder, by the DCC, for use in each CPCCRN study. Personnel at each Clinical Center are responsible to populate the binder with the relevant materials.

The Essential Documents Binder should be complete, well organized, and current. Materials can be filed elsewhere with a note of explanation placed in the binder, but it is intended that this binder serve as a directory to all study records and documents regardless of their physical location. Responsibility for maintaining the binder should be assigned to a specific individual. It is recommended that the binder be in a place where it is accessible to research staff for reference during their daily performance of duties.

3.4 Archiving Study Records

For CPCCRN studies funded by NHLBI or other Federal agencies, there are specific requirements for archival of study data.

For this study, the investigator must retain subject records in an easily retrievable form until disposal has been agreed in writing with the study sponsor. The investigator must have a ‘key’ linking the subject’s electronic data capture (EDC) number to the subject’s clinical file. If investigators move or retire, they must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a backup exists and a hard copy can be obtained from it if required.

3.5 IRB - Investigator Interactions

The IRB (IRB) is responsible for review of clinical research and protection of patient rights and welfare at each Clinical Center where research is undertaken. During all CPCCRN studies, the IRB or its equivalent at the Clinical Center is responsible, on behalf of the Clinical Center, to perform an ongoing review of the study.

The Principal Investigator at each Clinical Center must assure that the study is appropriately reviewed by a qualified IRB. Prior to initiating the

study, the investigator prepares an application for the IRB, in conformance with the requirements of the IRB. Depending on the type of study, this IRB application may include forms for informed consent, waiver of consent, compliance with the Health Insurance Portability and Accountability Act (HIPAA), protocol summaries, investigator biographies, and so forth. The format for IRB applications is different at each Clinical Center.

For CPCCRN studies, it is critical that the study protocol be identical at every Clinical Center. The local IRB application should refer to the CPCCRN study protocol, which should be included or attached to the local application. The CPCCRN study protocol may not be modified by the Clinical Center for its IRB application. If the IRB is unable to approve the CPCCRN study protocol, forcing alterations of the protocol, then the protocol must be modified by the CPCCRN for every Clinical Center in the study.

The Principal Investigator is responsible to assure annual review and approval of the study throughout its implementation and the publication of study results. The Clinical Center IRB must review a study at least annually, or more often at IRB discretion. The annual renewal must be sent to the DCC when it is received.

The Principal Investigator must report to the IRB all protocol violations if associated with unexpected risks to subjects and serious adverse events.

Whenever possible, DCC will notify investigators of items requiring IRB review, but it is the responsibility of the investigator to be familiar with local IRB requirements and to determine what items need to be reported to or approved by the IRB or its equivalent. The DCC will also attempt to remind Clinical Center investigators to renew the IRB approval for the project, but it remains the responsibility of the investigator at each Clinical Center to assure maintenance of local IRB approval for each study.

3.6 Clinical Center Site Inspections

In addition to the visit by a site monitor, a Clinical Center may be visited for an *inspection* by a local IRB auditor, NHLBI, FDA, or other auditor at various times during CPCCRN studies. The auditor is generally required to contact the investigator prior to the visit to arrange a mutually agreeable time. Following the visit, a site inspection report will be sent to the investigator summarizing findings and observations. All such reports should be filed separately from the Essential Documents Binder, but made available to the

DCC or the NHLBI as requested.

It is anticipated that site monitoring will be required for the CPCCRN ICU-RESUS. Regardless of whether a site monitoring visit actually occurs, Site *inspections* may be carried out by NHLBI, and Clinical Center investigators must be prepared to provide the materials described in this chapter.

3.7 Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for the DCC, NHLBI, or other Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When investigators sign the protocol, he/she agrees to allow the DCC, Drug Regulatory Agency and NHLBI auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his/her data will not be accepted.

The study sponsor is responsible for selecting qualified investigators, and has delegated responsibility to the DCC for ensuring proper monitoring of the investigation, and ensuring that the investigation is conducted in accordance with the general investigational plan and protocol. The CPCCRN network has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of the CPCCRN network. The DCC and NHLBI has Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that NHLBI sponsored studies are in accordance with the relevant Good Clinical Practices regulations/guidelines.

To accomplish these functions, the DCC and/or Regulatory Compliance at NHLBI selects investigational sites to audit. These audits usually take 1 to 2 days. The audits entail review of source documents supporting the adequacy and accuracy of data entered into the EDC system, review of documentation required to be maintained, and checks on drug accountability. The audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring the DCC and NHLBI of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives

- IRB approval
- Test article accountability
- Approved study protocol and amendments
- Informed consent of the parents/patients (parental permission/assent)
- Medical records supportive of Source Document data
- Reports to the IRB and the sponsor
- Record retention

The DCC and/or NHLBI will gladly help investigators prepare for an inspection.

Chapter 4

Data Safety Monitoring Board

The primary responsibility of the Data and Safety Monitoring Board (DSMB) is to ensure the safety of the patients.

- The DSMB will be composed of a minimum of three clinicians who have experience in clinical studies and one biostatistician with experience in the monitoring and analysis of clinical trials. None of the members will be investigators in the study.
- Guidelines for early termination of the study will be formulated by the DSMB at their first meeting prior to reviewing any data. The guidelines will be based on a group sequential monitoring plan agreed with the Steering Committee that preserves the overall alpha of the study and includes appropriate advisory boundaries for early stopping of the trial. This plan will be included in the DSMB Charter and immediately communicated to the Chairman of the Steering Committee. Upon satisfactory review by the Chairman, the Charter will be filed with the Chairman of the Steering Committee and NHLBI and the DSMB may then proceed with actual data review.
- The Chairman of the Steering Committee or necessary DCC members may be present at meetings of the DSMB at the invitation and discretion of the DSMB. This insures that various policy and operational matters can be appropriately discussed. In general, the DSMB will communicate to the network through the Chairman of the Steering Committee.
- The work of the DSMB will be conducted in strict confidence. Breaches of this confidence by any member of the DSMB will seriously undermine

the successful conduct and integrity of the trial, as well as its ultimate interpretation.

- The proceedings of each DSMB meeting, whether held face-to-face or as a teleconference, will be recorded in minutes. Copies of the minutes will be maintained by the Secretary of the DSMB, archived and kept confidential. Access to the minutes by the sponsor or study investigators will be prohibited until after the trial database has been locked and the study has been unblinded.

Chapter 5

Site Monitoring Visits

Contents

5.1	Monitoring by DCC	53
5.1.1	Site Monitoring Visits	53
5.1.2	Document Review During Site Monitoring Visits .	54
5.1.3	Remote Monitoring	56

5.1 Monitoring by DCC

A site monitor may visit each study site during the study period to review compliance with the study methodology and adherence to Good Clinical Practice (GCP) guidelines. General descriptions of the monitoring visits and items reviewed during site visits are included in this section. Throughout the duration of the ICU-RESUS study remote monitoring will be conducted. Remote monitoring will be discussed in this section.

5.1.1 Site Monitoring Visits

If the study requires site monitoring visits, the site will be contacted to ascertain a mutually agreeable visit date. Once the visit date has been decided, an announcement letter (Page 58) is sent to the site. The site monitor will outline what they will be reviewing in the announcement letter. However, the site monitor will not be limited to the outline in the announcement letter. For

instance, in addition to the items mentioned in the letter, the site monitor may ask to observe a mock consent process in order to better understand the consent process at the site.

Along with access to essential documents, the site monitor will expect provision for adequate workspace and access to the electronic data capture (EDC) system via the internet. The monitor will also expect to have access to key research personnel (e.g. the Clinical Center coordinator, and Clinical Center investigator) during the visit.

The Site Monitor will submit a visit report to the DCC, Clinical Center investigator and Clinical Center coordinator. If deficiencies are identified, the Clinical Center investigator is responsible for making corrections. Ultimately, in the unusual occurrence that the site does not respond to the recommendations to improve performance, the network leadership will discuss the appropriateness of the site's continued participation in the study protocol.

5.1.2 Document Review During Site Monitoring Visits

Essential Documents Please refer to Section 3.3 on page 45 for a detailed description of the essential documents required for this study. The Essential Documents Binder consists of all regulatory records and materials at the participating site pertaining to the study. These documents comprise the Clinical Center investigator's portion of what GCP terms "Essential Documents" for the conduct of a clinical study. These documents permit evaluation of regulatory compliance, conduct of the study, and the quality of the data produced.

The Essential Documents must be complete and well organized. The DCC may provide binders to each participating site to organize and file the regulatory documents, study correspondence and other essential documents using a format recommended for all DCC studies. Materials can be filed elsewhere with a note of explanation placed in this binder, but it is intended that this binder serve as a directory to all study records for documents contained in the binder and elsewhere.

All essential documents must be accessible at the time of the site monitoring visit. For instance, all original IRB correspondence, submissions, and attachments should be provided. Review of these items should provide clear documentation of consent revisions, protocol amendments and any correspondence with the IRB or any other regulatory body.

Source Document Verification A source document is the initial record of a data point. Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies). A certified copy is a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the attributes and information as the original. Types of source documents may include: protocol specific source documents, medical records, and notes to file.

If site monitoring is conducted during the study, access to the complete, original medical records and other applicable source documents at the site is required. This also pertains to remote monitoring; all source documents must be available to de-identify and submit to the DCC. Source documents will be compared to the data points entered in the EDC system.

If site monitoring is conducted at the site, it is imperative that sites confirm that there are no institutional restrictions to site monitor documentation access.

Data is transcribed from the source document to the EDC system. The EDC system contains each protocol specific data point. The site will maintain a patient study file referencing or containing each data point source that is entered in the EDC system.

The data point may be taken from protocol specific source documents. An example of this type of source document would be blood pressures taken at protocol specified time points which are not recorded in the medical record.

When a data point is taken from the medical record, a copy of the pertinent records may be placed in the patient study file. Although copies are not source documents, the copy will help direct you to the source data in the medical record for future queries or review. A certified copy from the electronic medical record is acceptable as a source document. To certify a copy of a medical record, ensure that the copy is an exact duplicate of the electronic medical record and has all of the attributes and information as the original. Sign and date the copy to indicate that the verification process was completed.

Another source document is the note-to-file. This note includes information that cannot be recorded elsewhere, it is not a data point per se, and usually requires a narrative. If the note-to-file documents a mistake or protocol violation made in the course of the study, a Corrective and Preventative Action (CAPA) form must be completed. This form provides an explanation

of the event along with a plan of action to ensure that it doesn't happen again. As with any source document, the note-to-file needs to be signed and dated by appropriate personnel and reference the subject (if applicable) and protocol.

In summary, all source documents need to be signed and dated by appropriate personnel, and all data points entered in the EDC system require a source document (protocol specific source documents, medical record, or note-to-file).

5.1.3 Remote Monitoring

In addition to on-site monitoring, the DCC has developed protocol specific quality assurance plans which include remote monitoring from the DCC. The main purpose of remote monitoring is to review data quality, verify that data elements are being drawn from the correct source documentation, and verify adherence to Good Clinical Practice guidelines.

In addition, documentation of remote monitoring submissions and correspondence must be maintained by the site in the Essential Documents Binder. If site monitoring is conducted, the site monitor will review remote monitoring documentation at the site and perform source document verification for a portion of the primary data points submitted to the DCC.

The DCC will send a letter (Page 59) to the clinical site requesting data be sent for remote monitoring. The letter will include EDC numbers on the participants to be monitored and a list of data points and/or source documents to be sent on the identified participants.

With the new options that have been offered for remote monitoring, sites can chose to use the steps outlined below, OR sites may facilitate DCC access to the local EMR or may review the study files in real-time via screen share.

1. The Clinical Center will respond by sending requested data to the DCC within 7 days of request. The Clinical Center should perform the following steps to send and identify documents appropriately:
 - Identify and gather source documents needed. Make a copy of source documents and de-identify this copy as is reasonably necessary by marking through provider and patient names either by-hand or electronically.
 - Write in the EDC number as close as possible to the top right corner, without obliterating underlying data.

- Upload requested documents along with original request to eRoomTM.
 - E-mail your DCC Project Manager when your documents have been uploaded to obtain acknowledgment of receipt.
 - Print out and place original DCC remote monitoring request letter, documents that were uploaded and acknowledgment of upload receipt from the DCC along with any other correspondence with the DCC in the Essential Documents (Regulatory) Binder. This documentation may be reviewed during on-site monitoring visits.
2. The DCC will review the documents sent from the Clinical Center and respond to the Clinical Center with a written report of data validation discrepancies or other issues identified within one month of upload receipt.
 3. The Clinical Center will have 21 days to respond to the written report by making corrections, submitting a CAPA, or re-uploading documents, as appropriate.
 4. The following will require re-uploading appropriate data to the DCC:
 - Source data is illegible.
 - Source data is not attributable to an individual subject and/or is not dated.



Data Coordinating Center
Collaborative Pediatric Critical Care Research Network

**PLEASE NOTE: THIS IS A SAMPLE ANNOUNCEMENT LETTER, THE REVIEW
ELEMENTS REQUESTED OF THE SITE MAY BE DIFFERENT.**

May 14, 2010

[Site PI]
[Site Study Coordinator]
[Address]
[E-mail]

Regarding: Site Monitoring for CPCCRN protocol 003 entitled "The Critical Illness
Stress-induced Immune Suppression Prevention Trial" (Short title: CRISIS Prevention)

Dear [Site PI]:

This letter is to confirm our appointment for the CRISIS Site Monitor interim visit to [Site Name]
on [Date(s)] and time of Site Monitor Visit].

The main purpose of this Site Visit will be to review and verify regulatory documents, verify
consent, and verify and review source documents. My visit will take [number of days of visit] full
days. With this in mind, please reserve a space (e.g. empty office or conference room) with
internet availability for me during these days.

Please have the following prepared:

1. Regulatory Document Binder
2. Essential Documents Binder
3. Informed Consent Forms on all subjects
4. Patient Study Files
5. Medical Records

If you have any questions or concerns, please feel free to contact me [Phone Number and email
address].

Sincerely,

[Site Monitor Name]
[Site Monitor Email Address]

cc via email: Jeri Burr, BS, RN-BC, CCRC, DCC Program Director

P.O. Box 581289

Salt Lake City, Utah 84158-1289 (801) 587-7609 Fax: (801) 587-7761



Data Coordinating Center
Collaborative Pediatric Critical Care Research Network

**PLEASE NOTE: THIS IS A SAMPLE LETTER, THE REVIEW ELEMENTS
REQUESTED OF THE SITE MAY BE DIFFERENT**

May 14, 2010

[Site Research Coordinator]
[Site Coordinator e-mail address]
Sent via Email

Regarding: Remote Monitoring for CPCCRN protocol 026 entitled "Measuring Opioid Tolerance Induced by Fentanyl (or Other Opioids)" (Short title: MOTIF Study)

Dear [Study Coordinator]:

This letter is being sent to officially request documentation for remote monitoring. Please respond within 7 days of this request.

For the following Trial DB numbers:

ST26[XXXX00XX]
ST26[XXXX00XX]
ST26[XXXX00XX]

Please follow instructions below to fax appropriate and attributable source documents for the following data points:

[Insert **only one** Data Group]

1. Identify and gather source documents needed. Make a copy of source documents and de-identify this copy as is reasonably necessary by marking through provider and patient names with a black felt marker.
2. Write in the Electronic Data Capture number as close as possible to the top right corner, without obliterating underlying data.
3. Fax requested documents along with original request to the DCC eRoom fax server at 801-587-8315.
4. Email Stephanie Bisping (stephanie.bisping@hsc.utah.edu) when your documents have been faxed to obtain acknowledgment of receipt.
5. Print out and place original DCC remote monitoring request letter, documents that were faxed and acknowledgment of fax receipt from DCC along with any other correspondence with DCC in Essential Documents (Regulatory) Binder. This documentation will be reviewed during on-site monitoring visits.

If you have any questions or concerns, please feel free to contact me.

Sincerely,
Stephanie Bisping

P.O. Box 581289

Salt Lake City, Utah 84158-1289 (801) 587-7609 Fax: (801) 587-7761

Chapter 6

Institutional Review Board and the DCC

Contents

6.1	Documentation of IRB Review	61
6.2	What If IRB Approval Is Denied?	62
6.3	Review Date Clarification	63
6.4	Consequences of Tardy Annual Review	64
6.5	Local IRB Amendments	64

6.1 Documentation of IRB Review

Documentation of initial IRB review and approval must be received by the DCC before a Clinical Center can begin patient enrollment or data submission for any CPCCRN study. The Clinical Center IRB must approve the study protocol. If any advertisements or posters will be used in the study, these should also be IRB approved and stamped. The documentation required by the DCC consists of the following:

- An approval letter signed by the IRB Chairperson (on Chairperson's official stationery) stating:
 - That participation in the study is approved

- The date or version number of the final protocol
 - Date of the IRB review/approval
 - Date of expiration
 - Any action or problems that the IRB noted
 - Amount of time spent on Facilitated Review in hours
- If the IRB did not note the version number or date of the protocol in the approval letter, the DCC will request the site to contact their IRB for a revised approval letter that includes the information listed above.
 - If the CPCCRN study involves informed consent, assent, advertisements, or other materials that require IRB approval, the DCC also requires documentation of approval of the specific items, either by having the IRB stamp the materials, or by explicit documentation in the letter from the IRB.

Documentation of annual IRB reviews must be sent to the DCC. If documentation is not received, sites will be unable to continue participation in the study (patient enrollment or data submission) until the documentation is received by the DCC . The documentation required for IRB annual renewal is the same as described above for the initial IRB review and approval. When CPCCRN studies involve informed consent, the DCC requests a copy of the approved informed consent form from each Clinical Center. If the consent form is translated into other languages, a copy of the translation and a letter from the certified translator should also be provided to the DCC .

6.2 What If IRB Approval Is Denied?

If a CPCCRN protocol is submitted to the Clinical Center IRB and not approved, do not alter the protocol in order to achieve approval. Identify whether the lack of approval is related to a component of the CPCCRN approved protocol, or whether the lack of approval is related to something in the other parts of the IRB application. In nearly all instances, lack of approval is related to something *outside* the underlying network study protocol.

For example, a CPCCRN approved study protocol might state that waiver of informed consent is requested because of reasons one, two and three. The

Clinical Center IRB may determine that informed consent should not be waived at the specific Clinical Center. The local application merely needs to indicate that informed consent will not be waived at that site. It is not necessary to alter the original CPCCRN study protocol. On the other hand, if the CPCCRN approved study protocol requires informed consent, the Clinical Center IRB may not reduce this requirement to waiver of consent. That is, a Clinical Center IRB may not reduce the human subjects protection required by the CPCCRN.

For another example, the Clinical Center IRB might require more details from local investigators concerning certain aspects of the study. These details may be provided in the application without necessarily being added to the underlying study protocol. The study protocol might indicate that data are submitted via secure electronic methods, but the Clinical Center IRB may require several pages of details. Such details can be provided in the IRB revised application, but are not added to the study protocol itself.

If the IRB refuses to approve a protocol and it is intrinsically related to material in the CPCCRN study protocol, then the CPCCRN will need to reevaluate the original protocol, for every Clinical Center, and the IRB approval process most often will have to be restarted at all sites. In this situation, it will be helpful if the Clinical Center IRB allows the CPCCRN to see the minutes of the discussion, to facilitate appropriate alteration of the study protocol.

6.3 Review Date Clarification

Renewal of Clinical Center IRB approval must take place on at least an annual basis, based on the date of the last approval.

Example 1. If the Clinical Center IRB approves the study on 1/15/00, then the renewal must take place on or before 1/14/01.

Example 2. If a study's initial IRB approval date is 1/15/00 and the annual renewal occurs on 1/8/01, then the next annual renewal would need to take place on or before 1/7/02.

If it is the policy of the Clinical Center IRB for the approval to take effect at the end of the month, then the next renewal can be accomplished anytime that month. In this case, the DCC must have a copy of that IRB's policy on file.

Example 3. If the IRB approved a study on 1/15/00, and it is the policy of that committee that the effective date will be the end of the month, then the approval date would be 1/31/00. Therefore, the next annual renewal can take place on or before 1/30/01.

Date of approval is the date the board or committee met, not the date of the Chairperson's signature.

6.4 Consequences of Tardy Annual Review

The DCC is prohibited by the University of Utah IRB from accepting study data from any Clinical Center that does not have IRB approval.

6.5 Local IRB Amendments

Amendments may occur at a Clinical Center for administrative reasons, such as a change in participating investigators. The Clinical Center Principal Investigator is responsible for adhering to the local Clinical Center IRB requirements. It is not required that the DCC receive IRB documentation concerning approval of revised investigators or insignificant administrative changes, as long as the CPCCRN study protocol itself is not amended.

In the event that the study protocol is amended by the CPCCRN in a non-administrative manner, the amendment will almost always require Clinical Center IRB approval, and the DCC will need to receive documentation of the IRB amendment approval.

Chapter 7

Investigator Responsibility

Contents

7.1	Investigator Qualifications and Agreements . . .	65
7.2	Communication with IRB	66
7.3	Compliance with Study Protocol	67
7.4	Protocol Amendments	67
7.5	Premature Study Termination	68
7.5.1	By Principal Investigator	68
7.5.2	By Clinical Center's IRB	68

7.1 Investigator Qualifications and Agreements

Principal Investigators, alternate PIs, and other participating investigators at Clinical Centers are personally responsible for all aspects of the clinical study, though it is evident that many activities are specifically delegated to other staff. This delegation of tasks is not a delegation of responsibility. It is important for each investigator to recognize the importance of careful supervision and oversight of all activities relating to a CPCCRN study. Some specific requirements for investigators engaged in human subjects research include:

- The Principal Investigator and all sub-investigators at the Clinical Center must be qualified by education, training and experience to

assume responsibility for the proper conduct of the study.

- All participating investigators at the Clinical Center must be aware of, and comply with, Good Clinical Practice (see Chapter 3 on page 43) and all applicable regulatory requirements. For CPCCRN studies involving the Food and Drug Administration (drug or device studies), each investigator must provide necessary regulatory documents to the DCC, including signed agreements acknowledging investigator responsibilities.
- The Principal Investigator and the Clinical Center *must permit* site monitoring and auditing by the CPCCRN DCC and the National Heart, Lung, and Blood Institute (NHLBI). For certain studies, inspections may be required and conducted by other Federal funding or regulatory agencies. Site monitoring is anticipated for the ICU-RESUS. This is described in more detail in Chapter 5 on page 53.
- The Principal Investigator or an alternate investigator at the Clinical Center must ensure that they have sufficient time to conduct and complete the study within the agreed upon study schedule.
- The Principal Investigator must have adequate staff and appropriate facilities that are available for the duration of the study and must ensure that other studies do not divert essential patients or facilities away from the study at hand.
- The Principal Investigator is responsible for reporting serious adverse events (SAE) that occur during a clinical study.
- The Principal Investigator and all collaborating investigators at the Clinical Center must ensure that all persons assisting with the study are adequately informed about the protocol, the investigational product (when applicable), and their study-related duties and functions.

7.2 Communication with IRB

Before initiating a study, the Principal Investigator must have written and dated approval from the IRB at the Clinical Center, for the study protocol, written informed consent forms, consent form updates, subject recruitment

procedures (e.g., advertisements), and any other written information to be provided to subjects, as applicable.

The Principal Investigator at the Clinical Center is responsible to assure renewal of IRB approval for all CPCCRN studies conducted at the Clinical Center, from onset of study through completion of final publication of study results.

7.3 Compliance with Study Protocol

The Principal Investigator and Clinical Center must conduct the study in compliance with the protocol agreed to by the CPCCRN protocol subcommittee, approved by the CPCCRN Steering Committee, approved by the NICHD Program Scientist, and approved by the IRB at the Clinical Center.

When a CPCCRN study protocol is modified, the Principal Investigator must assure that the local IRB is aware of the modification. Local IRB requirements will differ concerning requirements to file immediate amendments for such modifications, or to allow certain administrative changes to be submitted at the time of annual IRB review and renewal of approval.

The investigator must not implement any deviation from the approved protocol, nor make changes in the study protocol, without agreement by the CPCCRN protocol subcommittee, the DCC Principal Investigator, the NICHD Program Scientist, and the Clinical Center's local IRB.

Unintentional or intentional protocol deviations *do* occur during the course of nearly all studies. The investigator, or a person designated by the investigator, must document and explain any deviation from the approved protocol. Such documentation should be stored in the Essential Documents Binder, and may, according to local IRB policy, require IRB notification. In addition, the documentation should be transmitted to the CPCCRN DCC in order to assure proper analysis and interpretation of study data.

7.4 Protocol Amendments

No changes to the study protocol will be allowed unless agreed to by the CPCCRN protocol subcommittee, approved by the CPCCRN Steering Committee, approved by the NICHD Program Scientist, and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating center (and all participating centers) and will apply to all patients following approval as appropriate by each Institutional Review Board.

7.5 Premature Study Termination

7.5.1 By Principal Investigator

If the Principal Investigator terminates or suspends a study without prior agreement from the CPCCRN protocol subcommittee, the NICHD Program Scientist, and the Steering Committee, the investigator must promptly inform the CPCCRN DCC and the Clinical Center IRB. If this occurs, the investigator should provide a detailed written explanation of the termination or suspension to the CPCCRN DCC and the Clinical Center IRB. This written documentation, and all derivative correspondence, should also be stored in the Essential Documents Binder.

7.5.2 By Clinical Center's IRB

If the Clinical Center IRB terminates or suspends its approval of a study, the investigator must immediately (within 48 hours) notify the CPCCRN DCC. If this occurs, the investigator should provide a detailed written explanation of the termination or suspension to the CPCCRN DCC. The written documentation, and all derivative correspondence, should also be stored in the Essential Documents Binder.

Chapter 8

Staff Responsibilities

Contents

8.1	Staff Training	69
8.2	Screen Locations for Eligible Patients	70
8.3	IRB Approval	70
8.4	Maintain Essential Documents Binder	70
8.5	Document Responsibilities	70
8.6	Study Specific Staff Responsibilities	71

8.1 Staff Training

While the Principal Investigator and all collaborating investigators are ultimately responsible for all aspects of a CPCCRN study at a Clinical Center, many other staff will play significant roles in most studies. The Clinical Center Principal Investigator is responsible to assure that all staff have received adequate training to accomplish the tasks that have been delegated from the investigator to the staff member. Such training must be documented, and in certain studies, may require periodic repetition. For the current study, the Principal Investigator is responsible to assure that all Clinical Center staff involved have a clear understanding of the procedures in the study protocol and in this Manual.

8.2 Screen Locations for Eligible Patients

Staff may be assigned the task of screening patients as they present to the emergency department. For more detailed screening information relating to this study please refer to the Study Management Part of this MOO.

8.3 IRB Approval

Staff may be assigned the task of assisting the Principal Investigator in preparation and submission of IRB documents, but the investigator remains primarily responsible to assure IRB approval prior to initiation of the study, and annual renewal of the IRB approval throughout the life of the study (until all publications have been completed) or as specified by the local IRB.

8.4 Maintain Essential Documents Binder

Staff may be assigned the task of maintaining the Essential Documents Binder with up to date information.

8.5 Document Responsibilities

Delegation of responsibilities from the Principal Investigator to other personnel should be documented in writing in the Essential Documents Binder, as appropriate to the study.

Document the specific individual who is responsible for each of the study tasks. For example these may be:

- obtain and monitor local IRB approval and send copy of approval to DCC
- screen for eligible patients
- enroll patients
- maintain Essential Documents Binder

The Principal Investigator should sign and date this documentation of responsibilities. In many studies, especially interventional studies, it is desirable to

have each staff member provide signatures and initials for designated activities. This provides express acknowledgment of the delegation of responsibility and enables a site monitor to identify signatures and initials on study documents. On the next page, please find the suggested assignment of tasks as well as a template Documentation of Responsibilities form.

8.6 Study Specific Staff Responsibilities

Please complete Signatures and Delegated Responsibilities form to include all individuals who are participating in the study at each site and to which roles they oversee. Place this form in the Essential Documents Binder. Responsibilities should be study specific and delegated appropriately by the PI and might include:

1. Read and understand protocol and study procedures
2. Verify that all those required by the site IRB to complete Human Subjects training have certification on file
3. Submit study for site IRB approval
4. Maintain file of signature and delegated responsibilities forms
5. Train staff and maintain documentation of staff training
6. Maintain Essential Documents Binder (EDB) and Manual of Operations (MOO)
7. Screen patients for eligibility
8. Determine and verify patient eligibility
9. Patient Enrollment
10. Maintain tracking list of enrolled patients
11. Document eligibility
12. Submits ongoing IRB materials: Amendments, Continuations

Table 8.1: Signatures and Delegated Responsibilities

Name of Individual	Title or Position	Delegated Task	Signature	Initials	Effective Dates
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:

Principal Investigator Signature:

Date of Signature:

Part III

Study Management

Chapter 9

Study Workflow

Contents

9.1	Preparation	76
9.2	Definition of a CPR Event	77
9.3	Screening	77
9.4	Eligibility	78
9.5	Waiver of Consent	79
9.6	Transition & Implementation of Bundle	79
9.7	Data Collection	80
9.7.1	CPR Event Waveform Data	80
9.7.2	CPR Event Characteristics	81
9.7.3	<i>ETCO₂</i> Waveform Information	89
9.7.4	Post-CPR Event Hemodynamic Variables	89
9.7.5	PRISM & Glasgow Coma Scale	90
9.7.6	Demographics	91
9.7.7	Baseline FSS and PCPC	91
9.7.8	Hospitalization Information	92
9.7.9	Discharge FSS and PCPC	93
9.7.10	Death Data	93
9.7.11	ICU Information	93
9.8	Adverse Events	95

9.9 Additional Study Resources	95
9.9.1 Functional Status Scale	95
9.9.2 Pediatric Cerebral Performance Category	105

9.1 Preparation

In the ICU-RESUS, sites will be enrolling patients over a 4.5 year period. The overall workflow for the ICU-RESUS Study is as follows:

1. Screen PICU and CICU for CPR events.
2. Identify eligible index CPR events.
3. Collect and upload index CPR event waveform data.
4. Collect hemodynamic variables.
5. Collect index CPR event characteristic data.
6. Collect baseline FSS and PCPC data.
7. Collect PRISM data for designated time frame.
8. Collect demographic data.
9. Collect hospitalization data.
10. Collect ICU data.
11. Collect FSS and PCPC, upon hospital discharge.
12. Collect death data (as applicable).

9.2 Definition of a CPR Event

For the purposes of this study, a CPR event is defined as the administration of ANY chest compressions. A CPR event begins at the time the first chest compression is administered or "Hands on the Chest". A CPR event ends at the time the last chest compression is administered.

In this study, we are only interested in recording data for index events i.e. the first eligible CPR event within a hospital admission. Remember, part of the eligibility is that the event took place (or more accurately, started) inside the ICU setting. Subsequent or reoccurring events within the same hospital admission need not be recorded. If this patient is discharged from the hospital but then subsequently readmitted, and experienced another qualifying CPR event, then this would be considered as a separate index event. At the same time, if an event started outside of the ICU and continued into the ICU, then we would not enroll this event as it started outside of the ICU setting.

The outcome metric for *successful* CPR is ROSC for at least 20 minutes duration. The outcome metrics for *unsuccessful* CPR are transition to extracorporeal membrane oxygenation (ECMO) or death.

9.3 Screening

Once a Clinical Center (site) has IRB or CIRB approval, and study enrollment begins, screening for CPR events may begin. This study is unique in that screening occurs on an 'event' basis, rather than a 'patient' basis. This means that a patient may be eligible for study enrollment based upon one CPR event, and ineligible for study enrollment based upon another CPR event. It is possible for the same patient to have more than one eligible event across multiple hospitalizations.

The Pediatric Intensive Care Unit (PICU) and the Cardiac Intensive Care Unit (CICU) are the only two ICUs screened for CPR events. The screening process is highly individual (i.e. unique from site to site). Each site devises a thorough screening plan that ensures all CPR events within the PICU and

CICU are screened.

A screening log is used to track all screened CPR events. All eligible and ineligible CPR events are tracked on this log, for reference.

9.4 Eligibility

Once a research coordinator (RC) identifies a CPR event in the PICU or CICU, the RC will review the remaining inclusion and exclusion criteria to determine subject eligibility.

Inclusion criteria are:

1. Age ≥ 37 weeks and ≤ 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.

The Eligibility Worksheet is completed for all subjects meeting inclusion criteria (i.e., 'yes' is answered to both inclusion criteria). If a subject meets inclusion criteria in addition to any one of the exclusion criteria, data collection ends for this event, with the exception of indicating in which ICU the screening took place. If a subject meets all inclusion AND does not meet any of the exclusion criteria (i.e., 'yes' is answered to all inclusion and 'no' to all exclusion criteria), the subject is eligible for study enrollment. Once an eligible subject is identified, further data collection begins. **To reiterate, an eligible CPR event has all inclusion criteria marked 'yes' AND all exclusion criteria marked 'no'.**

The Eligibility Worksheet is the *only* worksheet that needs to be completed for an ineligible subject. See section [10.4.1 on page 111](#) for details on entering eligibility data in OpenClinica.

9.5 Waiver of Consent

Waiver of consent is requested for observational data collection for each event 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 enrollment period of the 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.

9.6 Transition & Implementation of Bundle

The hospitals which will be transitioning to the intervention (implementation of bundles) will be notified approximately 2 or 3 months before the scheduled implementation date. When each unit starts the program (i.e., the transition period), the goal is to have the debriefings every 3 weeks for the first 4 debriefings. Once 4 debriefings are completed (about 3 months), then the unit is considered to have "transitioned" to intervention. Once the first 4 debriefings are complete, the debriefings will be less often (approximately every 6 weeks so as to reach the minimum of 9 per year).

For sites with two units (PICU & CICU), the study can "tolerate" up to 4 combined debriefs per year i.e. 4 out of the 9 required debriefs can be shared between both units, with the remaining 5 being for each unit (5 PICU & 5 CICU). In such a situation, the site would be reimbursed for each of the combined debriefing as if two debriefs had been complete. Finally, to allow for the debriefings to have as extensive an exposure as possible, they should

not be held back to back on the same day, unless different participants are attending each.

9.7 Data Collection

Data collection is completed for all eligible CPR events. Data sources may include the CPR event ‘code sheet’, the electronic medical record (EMR), the bedside monitor, the clinical care team, and other potential sources. The following subsections describe specific data collection types and procedures, in detail.

9.7.1 CPR Event Waveform Data

Useable arterial line and $ETCO_2$ waveform data are collected starting 2 minutes prior to CPR and throughout the duration of the first 20 minutes of chest compressions. The RC consults with his/her Principle Investigator (PI) and/or an ICU MD to determine if waveform data are considered useable or not. In general waveform data needs to be able to be used to figure out the start and stop of CPR, cannot be truncated and needs to include the first minute of CPR. The RC obtains waveforms of the following variables, as available:

- Arterial diastolic pressure
- Arterial systolic pressure
- Central venous pressure/Right atrial pressure
- $ETCO_2$
- Electrocardiogram
- Plethysomography
- Pulse Oximetry
- Actual chest compressions provided per minute

Obtaining waveform data: It is critical to be aware of site-specific ICU bedside monitor data memory processes, so as not to lose any valuable waveform data. Bedside monitor data needs to be obtained prior to it being erased. It is possible that when a patient is transferred to another room or location, the bedside monitor data automatically erases. It is also possible that after a specific period of time passes (e.g., 24 hours, 72 hours, etc.) the bedside monitor data automatically erases. Obtaining the data before it is erased may involve calling the ICU or going there in person, soon after the CPR event occurs. Some sites' bedside monitors automatically sync with the EMR. In this situation, the RC may not *need* to obtain the data within a strict time frame.

Obtaining the waveform data involves printing it either directly from the bedside monitor, or from the EMR (if available from the EMR). Once printed, label (at least) the first page with the Subject ID Number and the EDC Occurrence Number. Keep in mind that these numbers will not be known until electronic data entry is started in OpenClinica. After obtaining the printed waveform data (and labelling it), schedule and complete the 'ICU RESUS Waveform & Defibrillation Data Upload Information' eCRF in OpenClinica. Then, upload the electronic copies of the waveform data to eRoom. See separate standard operating procedures in eRoom for further information related to the waveform upload process.

9.7.2 CPR Event Characteristics

CPR Event Characteristics data are recorded on the CPR Event Characteristics Worksheet. CPR event characteristics are data variables that directly relate to the CPR event at hand. The majority of these data variables are sourced from the event code sheet and/or the EMR. Speaking directly with the clinical care team is also an invaluable resource. RCs need to consult with the clinical care team and site PI if data is not readily available from the code sheet or EMR.

An explanation and/or definition is located beside each data variable below, as needed. The source of the definitions is: *Get With The Guidelines - Resuscitation PMT Coding Instructions, October 2012..*

- **Date of start of CPR event.** Date of the start of chest compressions.
- **Time of start of CPR event.** Time of the start of chest compressions (from the code sheet).
- **Interventions in place at time of CPR event.** Select each intervention that was *already in place* at the time of the start of the CPR event. Do not select interventions put in place at any time *during* the event. There is no limit to the number of interventions that can be selected.
 - **Vascular access** Includes peripheral vein, central vein, intraosseous (IO), umbilical vein (UVC), and umbilical artery (UAC)
 - **Arterial catheter**
 - **Central venous catheter**
 - **Vasoactive infusion** Includes dobutamine, dopamine $>3 \mu\text{g/kg/min}$, epinephrine, nitroglycerin, norepinephrine, phenylephrine, vasopressin, and other vasoactive agents.
 - **Invasive mechanical ventilation** Includes mechanical ventilation via endotracheal tube, tracheostomy, or laryngeal mask airway. Includes T-piece, assist control, IMV, pressure support, high frequency, and other. Nasopharyngeal and oropharyngeal airways are NOT considered invasive airways.
 - **ETCO₂ monitoring**
 - **Non-invasive ventilation** Includes Bag-Valve-Mask, Mask CPAP/BiPAP, Nasal CPAP/BiPAP, and negative pressure ventilation.
- **Conditions present at time of CPR event.** Select each condition that was *already present* at the time of the start of the CPR event. There is no limit to the number of conditions that can be selected.
 - **Respiratory insufficiency.** Defined by ANY of the following:
 - * PaO_2/FiO_2 ratio <300 (in the absence of pre-existing documented cyanotic heart disease).

- * $PaO_2 < 60$ mmHg (in the absence of pre-existing documented cyanotic heart disease).
- * $SaO_2 < 90\%$ (in the absence of pre-existing documented cyanotic heart disease).
- * $PaCO_2$, $ETCO_2$, or $TcCO_2 > 50$ mmHg.
- * Ages 18+ years - spontaneous respiratory rate $> 40/\text{min}$ or $< 5/\text{min}$.
- * Ages 9-17 years - spontaneous respiratory rate $> 50/\text{min}$ or $< 5/\text{min}$.
- * Ages 1-8 years - spontaneous respiratory rate $> 60/\text{min}$ or $< 5/\text{min}$.
- * Age < 1 year - spontaneous respiratory rate $> 60/\text{min}$ or $< 10/\text{min}$.
- * Requiring non-invasive ventilation (e.g., Bag-Valve-Mask, Mask CPAP/BiPAP, Nasal CPAP/BiPAP, negative pressure ventilation).
- * Requiring ventilation via invasive airway (e.g., T-piece, assist control, IMV, pressure support, high frequency).

– **Hypotension.** Defined by ANY of the following:

- * Adult (18+):
 - SBP < 90 or MAP < 60 mmHg.
 - Vasopressor/inotropic requirement after volume expansion (except for dopamine $\leq 3 \mu\text{g}/\text{kg}/\text{min}$).
 - Intra-aortic balloon pump.
- * Pediatric (< 18):
 - SBP $< 5\text{th}$ percentile for age, less than $[70 + 2 \times \text{age in years}]$ for age < 10 .
 - MAP $< 5\text{th}$ percentile for age.
 - Vasopressor/inotropic requirement after volume expansion (except for dopamine $\leq 3 \mu\text{g}/\text{kg}/\text{min}$).
- * Newborn/Neonate:
 - Documentation/evidence of symptomatic hypotension/hypoperfusion.

- **Congestive heart failure.** Defined by documented diagnosis of congestive heart failure.
- **Pneumonia.** Defined by documented diagnosis of pneumonia where antibiotics have not yet been started or the infection is still being treated with antibiotics.
- **Sepsis.** Defined as documentation of sepsis in the patient's medical record.
- **Trauma.** Defined by documented evidence of multi-system injury or single system injury associated with this hospitalization.
- **Renal insufficiency.** Defined by ANY of the following:
 - * Adult (18+):
 - Requiring ongoing dialysis or extracorporeal filtration therapies.
 - Creatinine >2 mg/dL within 24 hours up to the time of the event.
 - * *Pediatric (<18):*
 - Requiring ongoing dialysis or extracorporeal ultrafiltration therapies.
 - If <30 kg: Oliguria (urine output <1 ml/kg/hr for >8 hrs) and creatinine >1 mg/dL within 24 hours up to the time of the event.
 - If >30 kg: Oliguria (urine output <0.5 ml/kg/hr for >8 hrs) and creatinine >2 mg/dL within 24 hours up to the time of the event.
- **Malignancy.** Defined by a documented malignancy.
- **Congenital heart disease.** Defined by documented diagnosis of congenital heart disease
 - * **If yes, select all applicable CHD below** Select all CHDs that apply

- * **Has the subject undergone cardiac surgery at any time prior to arrest**
 - **If yes, specify the most recent surgical palliation prior to time of arrest** Here we are only interested in the most recent cardiac surgery that the above question referenced.
 - **If either BT shunt is selected, following the arrest was the shunt found to be occluded** This can be found by review of echocardiogram, catheterization, CT scan, operative report, or autopsy.
 - **Date of last cardiac surgical intervention** The date of the intervention detailed above
 - **If date of last cardiac surgical intervention is the same as date of arrest, did the arrest occur prior to surgical intervention** In instances where the date recorded above and the date of the cardiac arrest are one and the same, we would like to know which came first. Select "Not Applicable" if the dates are not the same.
- **Pulmonary Hypertension.** Defined by a documented hospital diagnosis:
 - * **If yes, are they being treated with any of the medication listed below.** If they have Pulmonary Hypertension but are not receiving any of the drugs listed below, select "Not being treated with any of the drugs listed"
 - **Ambrisentan**
 - **Bosentan**
 - **Eproprostiril**
 - **Iloprost**
 - **Macisentan**
 - **Riociguat**
 - **Selexipag**
 - **Sildenafil**
 - **Sitaxsentan**
 - **Tadalafil**

- Treprostinil
- Vardenafil
- Not being treated with any of the drugs listed
- * If yes, is there an active order for iNO
 - Indicate the primary organ system dysfunction leading to iNO initiation (Cardiac vs Respiratory)
- **Immediate cause(s) of CPR event.** Select each cause of the CPR event. Consult with the site PI for guidance with this question. There is no limit to the number of causes that can be selected.
 - Hypotension
 - Respiratory decompensation
 - Arrhythmia (VF, VT, SVT)
 - Cyanosis without respiratory decompensation
- **Was the CPR event during or within 20 minutes of endotracheal intubation?**
- **Was it a witnessed cardiac event?** Was the onset of the cardiac event observed by someone (family member, lay bystander, employee, health care professional, monitor technician, etc.)? If someone finds the patient already deceased, it was not a witnessed event.
- **Was the sternum closed at the onset of the CPR event?**
- **Was the sternum opened during the CPR event?**
- **Date and time the sternum was opened.** (if applicable)
- **What was the first documented rhythm at the time CPR was initiated?** Select one option from the choice set below. The first documented rhythm is most likely sourced from the event code sheet.

Select the first documented rhythm at time of, or after, initiation of chest compressions. Consult with the site PI for guidance with this question.

- Ventricular fibrillation (VF)
 - Pulseless electrical activity (PEA)
 - Bradycardia with pulses
 - Ventricular Tachycardia (VT)
 - Asystole
-
- **Date and Time first shockable rhythm was determined.** The first shockable rhythm is most likely sourced from the event code sheet. Indicate the first shockable rhythm after the initiation of chest compressions. The time of the first shockable rhythm will most likely be immediately followed by the first attempted defibrillation. Consult with the site PI for guidance with this question.

 - **Date and Time of first attempted defibrillation for shockable rhythm.** The time of the first attempted defibrillation for a shockable rhythm is most likely sourced from the event code sheet. The time of the first attempted defibrillation for a shockable rhythm will most likely be immediately after the time the first shockable rhythm was determined.

 - **Time of first bolus administration of vasopressor medication.** This *only* refers to a bolus of either epinephrine or vasopressin.

 - **Medications administered during the CPR event.** Select each medication administered during the CPR event. There is no limit to the number of medications that can be selected. Do not document any medications beyond this list. An ‘other’ option was purposely omitted from the choice set below.
 - epinephrine

- * **Total number of epinephrine doses.** Record the total number of epinephrine doses administered during the CPR event.
 - atropine
 - calcium
 - sodium bicarbonate
 - vasopressin
 - amiodarone
 - lidocaine
 - fluid bolus
- **Date of end of CPR event.** Date of the end of chest compressions.
- **Time of end of CPR event.** Time of the end of chest compressions (from the code sheet).
- **Outcome of the CPR event.** Select one option from the choice set below. If unsure of the event outcome, consult with the clinical care team and the site PI.
 - **ROSC $\geq$ 20 minutes**
 - **Transitioned to ECMO**
 - **Died.** Defined by: Efforts terminated, no sustained return of circulation (ROC): Effort terminated; the patient did not respond to Advanced Life Support (ALS), unable to achieve sustained ROC, or there was an advance directive limiting ALS, or there were restrictions placed by the family of the patient during the event (i.e. family requested event be terminated).
- **ECMO within 24 hours** This question is to catch patients that may have gotten ROSC without ECMO initially, but within the next 24 hours subsequently decompensated enough to require ECMO support post ROSC.

9.7.3 *ETCO₂* Waveform Information

This data can be sourced from the event code sheet and/or the electronic medical record. If *ETCO₂* waveform data are submitted and determined to be useable following a clinical review by the Children's Hospital of Philadelphia, the following data will be collected:

- **Intervention in place at the time of CPR event**
 - **Pulse oximeter** Includes documenting location of the device.
 - **Invasive airway** Includes documenting if airway was cuffed at last documentation or was placed during the arrest.
 - **Inhaled nitric oxide** Includes documenting peak dose during CPR or was started during the arrest.
 - **Epinephrine infusion** Includes documenting peak dose during CPR, date and time dose was changed to peak dose, or if an infusion was started during the arrest.
- **Pharmacologic interventions given during CPR**
 - **Vasopressors** Document date, time and dose of all vasopressors given during CPR. This includes epinephrine, vasopressin, isoproterenol, phenylephrine, or other.
 - * **Other** Only document other vasopressors not listed above in this field. Additional pharmacologic interventions during CPR **DO NOT** need to be recorded.
 - **Sodium Bicarbonate** Document date, time and dose of any sodium bicarbonate given during CPR.

9.7.4 Post-CPR Event Hemodynamic Variables

This information is collected during two separate windows. The first window is the 6 hours immediately post-CPR event. The second window is from 6 to 24 hours post-CPR event. The following data is collected:

- **Highest and Lowest invasive systolic and diastolic blood pressure**

- Highest and Lowest non-invasive systolic and diastolic blood pressure
- Highest and Lowest core and non-core temperatures
- Highest and lowest PaO₂ (arterial only)
- Highest and lowest arterial and venous PCO₂
- Highest and lowest arterial and venous pH
- Highest arterial and venous lactate
- Highest and lowest blood glucose (can be venous or arterial)
- Highest and lowest pulse oximetry

9.7.5 PRISM & Glasgow Coma Scale

This worksheet is to be populated with values obtained during the following 4 hour time frame: 6 hours prior to CPR event up to 2 hours prior to the CPR event. Data collected includes:

- Lowest value for systolic blood pressure
- Highest value for heart rate
- Highest and lowest values for temperature
- Glasgow Coma Scale assessment
 - Eye Response
 - Verbal Response
 - Motor Response
- Highest and lowest value for pH (arterial preferred but venous otherwise)
- Lowest value for PaO₂ (only arterial)
- Highest value for PCO₂ (arterial preferred but venous otherwise)

- **Highest and lowest total CO2**
- **Highest serum glucose, serum potassium, creatinine and BUN**
- **Lowest value for WBC and Platelets**
- **Highest value for PT & PTT**

9.7.6 Demographics

Demographic information is documented on the Demographics Worksheet. The following demographic data is collected:

- **Date of birth**
- **Sex**
- **Ethnicity** Some sites do not collect ethnicity, only race. If Hispanic or Latino is documented as a race in the medical record, it should be documented under ethnicity on the Demographics Worksheet, and race should be documented as “unknown or not reported.”
- **Race**
- **Patient’s weight.** Record weight used during the CPR event and recorded on the code sheet. May use weight from EMR if not available from code sheet.
- **Patient’s height.** Record height from code sheet, if available. May use height from EMR if height is not available from code sheet.

9.7.7 Baseline FSS and PCPC

A ‘baseline’ Functional Status Scale (FSS) assessment and Pediatric Cerebral Performance Category Scale (PCPC) assessment are collected and reflect the patient’s status (in *most* cases) prior to the event that lead to the hospitalization(s). The ‘baseline’ FSS and PCPC are reasonable assessments of the patient’s neurological status prior to the arrest.

In some cases, the baseline FSS and PCPC assessments will not reflect the patient’s status prior to the event that lead to the hospitalization. For

example, if the patient has been living in the hospital for 1 year, we want to know what the neurological status was prior to the decompensation associated with the cardiac arrest. Saying that, if a patient is hospitalized for a period of over 90 days, then the baseline will be assessed no further back than 30 days prior to the cardiac arrest event, while not including assessments done during the first 24 hours prior to the event.

If a patient is born during the same hospitalization in which the CPR event occurred and has been in the hospital for less than 90 days at the time of event, the baseline status will be recorded as normal. If they have been in hospital for more than 90 days, then baseline will be assessed no further back than 30 days prior to event.

Complete these assessments by discussion with the clinical care team, rather than by referencing the EMR. Discussion with the clinical care team and the site PI is the preferred method for obtaining the patient's baseline status. If needed, Dr. Sutton is available for consultation on a case by case basis. See section 9.9 on page 95 for definitions related to assessing FSS and PCPC.

9.7.8 Hospitalization Information

Hospitalization information is documented on the Hospitalization Summary Worksheet. The following hospitalization data is collected:

- **Was this patient enrolled in the ICU-RESUS study during a previous hospitalization**
 - If yes, original OpenClinica Subject ID Number Document the OpenClinica Subject ID Number for which the patient was first enrolled in this study. A patient may have multiple eligible CPR events across multiple hospitalizations.
- **Hospital admission date and time**
- **Hospital discharge date and time**
- **EEGS** Include any EEG that was performed in the 72 hours after the event.

- **Head Imaging** Include any head imaging that took place in the 168 hours after the event. This includes but is not limited to head ultrasound, MRI and CT scan.
- **Vital Status at discharge**
- **Limitations of Care** Immediately following the cardiac arrest event and CPR, were any limitations put into place for any of the listed interventions (such as DNR or otherwise). If subject continued for a period of time without any limitations and then it was decided to redirect care and place them under DNR, the answer would still be no.

9.7.9 Discharge FSS and PCPC

‘Discharge’ FSS and PCPC are collected upon hospital discharge, and reflect the patient’s status at those time points. Complete these assessments by discussion with the clinical care team, rather than referencing the EMR. Discussion with the clinical care team is the preferred method for obtaining the patient’s discharge status. See section [9.9 on page 95](#) for definitions related to assessing FSS and PCPC.

9.7.10 Death Data

Death information is documented on the Hospitalization Summary Worksheet. The following death data are collected:

- **Vital status at hospital discharge**
- **Death date and time**
- **PCPC** If the patient died, the PCPC assessment is marked ‘brain death.’ The FSS assessment does not need to be completed upon patient death. See section [9.9 on page 95](#) for definitions related to assessing PCPC.

9.7.11 ICU Information

ICU Information is documented on the ICU Information Worksheet. The ICU stay, in which an index CPR event occurs, is documented. An ICU stay

in which no index CPR event occurred, or in which an ineligible CPR event occurred, is not documented. The following ICU data is collected:

- **ICU admission date and time**
- **ICU Illness Category** Select one ICU illness category from the choice set below. The source of definitions is, *Get With The Guidelines - Resuscitation PMT Coding Instructions, October 2012*.
 - **Medical cardiac** Patient with a primary diagnosis of medical illness that is cardiovascular at the time of the event.
 - **Medical non-cardiac** Patient with a primary diagnosis of medical illness at the time of the event that is not cardiovascular.
 - **Surgical cardiac** Patient who is post-operative following cardiac surgery at the time of the event.
 - **Surgical non-cardiac** Patient who is post-operative or post-operative with a surgical illness as the primary diagnosis that is not cardiac surgery at the time of the event.
 - **Trauma** Patient with single or multiple trauma(s) as the primary diagnosis at the time of the event.
- **ICU discharge date and time**
- **Previous in-hospital arrest associated with this ICU admission**

This question is attempting to get at any arrests that happened right before this ICU admission, excluding arrests in the OR during cardiac surgery (which are considered part of the OR procedure and is NOT considered “a previous in-hospital arrest”).

Hence, answer with “No” if this is the patient’s first cardiac arrest inside a hospital (in the scope of this admission) or if the only cardiac arrest they had previously was in the OR during cardiac surgery.

“Current admitting network hospitals” include all hospitals participating in the ICU-RESUS study.

9.8 Adverse Events

Adverse events will not be collected in this study as it is an observational study with no therapeutic interventions.

9.9 Additional Study Resources

This section includes the following additional study resources:

1. Functional Status Scale (FSS)
2. Pediatric Cerebral Performance Category (PCPC)

9.9.1 Functional Status Scale

The following information was adapted from:

Pollack M, Holubkov R, Glass P, Dean J, Meert K, Zimmerman J, Anand K, Carcillo J, Newth C, Harrison R, Willson D, Nicholson C, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. The Functional Status Score: A new pediatric outcome measure. *Pediatrics* 2009;124:e18-28

CPCCRN 048: BATE

Functional Status Scale					
	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	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 <u>and</u> to visual stimuli	Abnormal responses to pain or touch
Communication	Appropriate non-crying 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 Function	Coordinated body movements, normal muscle control, and awareness of action and reason	1 limb functionally impaired	2 or more limbs functionally impaired	Poor head control	Diffuse spasticity, paralysis, <u>or</u> 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	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

MENTAL STATUS

Normal

- Normal sleep and wake periods;
- Appropriate social responsivity

Sleep refers to a restful state without over-reaction (crying, agitation) to noises in the environment. Awake refers to awareness with behavior appropriate for age. Infants and children in this state should be appropriately aware, alert and responsive of self and environment.

Mild Dysfunction

- Sleepy but arousable to noise or touch or movement, and/or
- Periods of reduced social responsivity

Sleeps more of the time than is age appropriate; will sleep much of the time if left alone but is able to be aroused with stimulation such as noise, if touched or position changes. Alternatively, decreased responsiveness to social overtures and/or does not consistently focus on or follow a person or object crossing the line of vision.

Moderate Dysfunction

- Lethargic and/or
- Irritable

Lethargic infants and children are drowsy, sluggish, or have an unusual lack of energy. They are arousable, but become less responsive or return to a sleep-like state without frequent stimulation. Irritable infants and children are inconsolable often with an increased sensitivity to stimulation. Infants often react to stimuli with a high-pitched cry.

Severe Dysfunction

- Minimal arousal to stimulus (stupor)

Stuporous infants and children have decreased or impaired consciousness marked by diminution in reactions to environmental stimuli. They may open eyes and focus, but do not maintain any meaningful reaction to physical environment. They make little or no eye contact. They will respond to noxious stimuli with semi-purposeful (i.e. poorly organized) movements or withdrawal.

Very Severe Dysfunction

- Unresponsive and/or
- Coma and/or
- Vegetative

These infants and children are unconscious. Coma is a deep or profound state of unconsciousness from which they cannot be aroused. They do not sense or respond to external stimuli or internal needs. Vegetative infants and children have no evidence of awareness of self or environment. They may have intermittent wakefulness manifested by sleep- wake cycles. There is no evidence of sustained, reproducible, purposeful or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli.

SENSORY**Normal**

- Intact hearing, and
- Intact vision, and
- Responsive to touch or pain

Intact hearing is demonstrated by individuals localizing/ moving eyes and/or head toward sound stimulus in room. Intact vision is evidenced by individuals turning gaze to focus on person or object that crosses his visual field.

Mild Dysfunction

- Suspected hearing loss, or
- Suspected vision loss

There is suspicion of hearing or vision loss as evidenced by inconsistent focusing or localization of sound. Responsiveness to touch is not impaired.

Moderate Dysfunction

- Not reactive to auditory stimuli, or
- Not reactive to visual stimuli

There is lack of evidence for hearing or vision as demonstrated by lack of focusing, or localization of sound. Responsiveness to touch is not impaired.

Severe Dysfunction

- Not reactive to auditory stimuli, and
- Not reactive to visual stimuli

There is lack of evidence of hearing or vision as evidenced by lack of tracking, and localization of sound. Responsiveness to touch is not impaired.

Very Severe Dysfunction

- Abnormal response to touch or pain

Infant/child has abnormal response to touch or pain as evidenced by the absence of purposeful, or semi-purposeful movements. There may be a withdrawal or spinal response.

COMMUNICATION

Normal

- Vocalization appropriate for age, and
- Interactive facial expressions or gestures.

Infants make sounds to make presence known. Children use words to convey needs. Interactive facial expressions and gestures are a process of non-verbal communication, often closely associated with emotions.

Mild Dysfunction

- Diminished vocalization
- Diminished social expression - facial or verbal

There is a decrease in socialization and social expression.

Moderate Dysfunction

- Absence of attention-getting behavior

Infants and children who do not demonstrate behavior that “says” “look at me, here I am.” Children may initiate attention-getting behavior, but cannot communicate their needs.

Severe Dysfunction

- No demonstration of discomfort

Infants and children do not cry or cry very little with painful procedures or if uncomfortable.

Very Severe Dysfunction

- Absence of communication.

There is no communication using facial expressions, body posture, or voice. There is no communication regarding physiological or psychological needs.

MOTOR FUNCTIONING**Voluntary movements: Normal**

- Coordinated body movements, and
- Normal muscle control, and
- Awareness of action

Infants and children have coordinated movements with normal muscle control. They are aware of the action and its purpose (e.g., infant kicks limbs, vocalizes when parent enters.) Infant can hold rattle and transfer it from one hand to another. Toddler carries object, holds onto stuffed animal, sucks thumb. Child writes or plays with toys.

Mild Dysfunction

- 1 limb functionally impaired

There is a partial or complete loss of functionality of the limb. Impairment may be from a medical device such as a soft or hard restraint, arm board for IVs, bandage, cast, or due to physical and medical issues such as deformity, weakness, stiffness, spasticity, and/or movement disorders. Weakness is demonstrated when infants and children are able to move the limb off a surface (against gravity) while holding an object or against resistance. They may be able to perform normal age appropriate activities but with increased effort. Stiffness is demonstrated when the limb has increased resistance to passive motion but is still held in a normal position or posture. Stimulation does not result in flexion, extension or arching. Spasticity is abnormally

increased muscle tone with involuntary movement. The limb feels tight, rigid and limb reflexes are exaggerated. There is resistance to bending and the neck is hyperextended.

Moderate Dysfunction

- 2 or more limbs functionally impaired

There is a partial or complete loss of functionality of 2 or more limbs. Impairment may be from medical devices such as soft or hard restraints, arm boards for IVs, bandages, casts, or due to physical and medical issues such as deformities, weakness, stiffness, spasticity, and/or movement disorders. Weakness is demonstrated when infants and children are able to move limb off a surface (against gravity) while holding an object or against resistance. They may be able to perform normal age appropriate activities but with increased effort. Stiffness is demonstrated when one or more limbs have increased resistance to passive motion but are still held in normal position or postures. Stimulation does not result in flexion, extension or arching. Spasticity is abnormally increased muscle tone with involuntary movement. Limb(s) feel tight, rigid and limb reflexes are exaggerated. There is resistance to bending and the neck is hyperextended.

Severe Dysfunction

- Poor Head Control

Head control is poor with decreased ability to hold head upright at 90°. Unable or cannot hold head still when less than 90°. If trunk is supported head will fall back, to side or front and he/she is unable to bring head to the upright position if sitting or midline if supine or prone.

Very Severe Dysfunction

- Paralyzed
- Decerebrate/Decorticate Posturing

Paralysis is the loss of voluntary motor function. There is abnormal muscle tone. Mental Status may be preserved or altered. Decerebrate posture consists of rigid extension of all extremities with internal rotation. There is downward pointing of toes. Decorticate posture consists of rigid flexion of upper extremities with clenched fists and extension of lower extremities.

FEEDING

Normal

- All food taken PO with age appropriate help.

There is no parenteral or gavage feeding. Feeding methods are age appropriate. Caloric intake is not a classification criterion for this category.

Mild Dysfunction

- NPO, or
- Need for age-inappropriate help with oral feeding

There is no parenteral nutrition or tube feeding. (Dextrose solutions of 5% or less are not considered parenteral nutrition). Examples of age-inappropriate feeding include feeding by a caretaker when independent feeding is expected or when a feeding aid such as a bottle is used at an inappropriate age.

Moderate Dysfunction

- Tube feedings with or without additional oral intake

Tube feedings include nutrition via a nasogastric, oral-gastric, or small bowel tube. There is no parenteral nutrition. (Dextrose solutions of 5% or less are not considered parenteral nutrition).

Severe Dysfunction

- Parenteral nutrition in addition to oral or tube feeding.

Parenteral nutrition includes intravenous nutrition via a peripheral or central vein with a dextrose concentration greater than 5%. It usually includes fat and protein.

Very Severe Dysfunction

- All nutrition is parenteral

Parenteral nutrition includes intravenous nutrition via a peripheral or central vein with a dextrose concentration greater than 5%. It usually includes fat and protein. Child is unable to tolerate *any* enteral feeds, whether by mouth or tube feedings.

RESPIRATORY STATUS**Normal**

- Room air and no artificial support or aids

The infant or child is breathing in room air without the need for artificial help including suctioning, oxygen, or mechanical support.

Mild Dysfunction

- Oxygen, and/or
- Suctioning

Oxygen given via any apparatus including blow-by, cannula, face mask, etc. Suctioning includes any oral or tracheal suctioning.

Moderate Dysfunction

- Tracheostomy

Severe Dysfunction

- CPAP for all or part of the day, and/or
- Mechanical ventilator support for part of the day

CPAP (continuous positive airway pressure) may be administered through a facemask or tracheostomy. Mechanical support includes positive or negative pressure ventilation devices such as bipap, and positive pressure mechanical ventilation.

Very Severe Dysfunction

- Mechanical ventilatory support for all day and night.

Mechanical support includes positive or negative pressure ventilation devices such as bipap, and positive pressure mechanical ventilation.

9.9.2 Pediatric Cerebral Performance Category

The following information was adapted from:

Fiser DH, Long N, Roberson P, Hefley G, Zolten K, Brodie-Fowler M. Relationship of Pediatric Overall Performance Category and Pediatric Cerebral Performance Category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. *Crit Care Med* 2000;28:7(2616-2620).

CPCCRN 048: BATE

Pediatric Cerebral Performance Category Scale (PCPC)	
Normal (score = 1)	*Age-appropriate level of functioning *Preschool child: developmentally appropriate *School-aged child: attends regular school classroom
Mild Disability (score = 2)	*Conscious, alert, and able to interact at age-appropriate level *Preschool child: may have minor developmental delays *School-aged child: attending regular school classroom, but grade is not appropriate for age, or child is failing appropriate grade because of cognitive difficulties *Possibility of mild neurologic deficit or mild neurologic disease that is controlled and does not interfere with daily functioning (i.e. seizure disorder)
Moderate Disability (score = 3)	*Conscious; below age-appropriate functioning *Neurologic disease that is not controlled and severely limits activities *Preschool child: delayed for most of their activities of daily living *School -aged child: sufficient cerebral function for age-appropriate independent activities of daily life; attending special education classroom because of cognitive difficulties and/or learning deficits
Severe Disability (score = 4)	*Conscious *Preschool child: delayed for most of their activities of daily living and excessively dependent on others for the provision of activities of daily living *School-aged child: may be so impaired as to be unable to attend school; dependent on others for daily support because of impaired brain function
Coma/vegetative (score = 5)	*Any degree of coma *Unaware, even if awake in appearance, without interaction with environment *Cerebral unresponsiveness and no evidence of cortical function (i.e. not aroused by verbal stimuli) *Possibility of some reflexive response, spontaneous eye-opening and sleep-wake cycles
Brain death (score = 6)	*Apnea, areflexia, and/or electroencephalographic silence
General guidelines for determining level of impairment: Normal: Child has no disability or medical conditions and is functioning appropriately Mild Disability: Child has minor delays or functional impairments and most skills are within age-appropriate limits, or the child has well-controlled medical conditions Moderate Disability: Child is significantly delayed or functionally impaired in most areas, but demonstrates some level of independence in activities of daily living Severe Disability: Child is responsive to the environment but dependent on others for daily support because of impaired brain functioning or other medical condition (not age) Coma/vegetative: Child has any degree of coma, is unaware and unresponsive, even if awake in appearance, without interaction with environment Brain death: Child has apnea, areflexia, and/or electroencephalographic silence	

Chapter 10

Data Management

Contents

10.1 Data Entry Contact for Questions	108
10.2 Global Data Entry	108
10.3 Study Events and Electronic Case Report Forms	109
10.4 eCRF Specific Data Entry Guidelines	111
10.4.1 Eligibility	111
10.4.2 CPR Event Characteristics	111
10.4.3 Post-CPR Event Care Variables	111
10.4.4 PRISM	112
10.4.5 Vasoactive Inotropic Score	112
10.4.6 Waveform and Defibrillation Data Upload Infor- mation	112
10.4.7 CPR Later Found to be Unnecessary	112
10.4.8 <i>ETCO₂</i> Waveform Information	113
10.4.9 Demographics and Physical Measurements	113
10.4.10 Baseline Functional Assessments	113
10.4.11 Hospitalization Summary	113
10.4.12 ICU Dates and Other Information	113
10.5 Survey Data Entry	113

10.1 Data Entry Contact for Questions

If you have questions regarding OpenClinica eCRF data entry, or anything related to Clinical Data Management for this study, please contact the Clinical Data Manager for this study:

Melissa Pederson, MEd
Clinical Data Manager
CPCCRN Data Coordinating Center
melissa.pederson@hsc.utah.edu
801-213-3352

10.2 Global Data Entry

OpenClinica is the primary electronic data capture (EDC) system that will be used for this study. The following key points apply to entering data in OpenClinica, for the following types of fields:

Study Subject ID: Upon clicking ‘Add Subject, the Study Subject ID on the screen will be pre-labeled with ‘ID will be generated on Save or Add.’ When the new subject is added, the next sequential study number available will become the Study Subject ID. This field is neither editable nor configurable. Each subject added in OpenClinica will have a unique Study Subject ID. This means that across studies and across sites, no two subjects will share the same Study Subject ID.

Date Fields: Dates must be entered in DD-MMM-YYYY format, with MMM being the 3 letter English month abbreviation with only the first letter capitalized, i.e. Jan, Feb, Mar, Apr, May, etc. Dates not entered in this format cannot be saved. You will know the date field requires a full date by the units specified in parentheses.

Time Fields: Times must be entered in HHMM military time format. The valid range for times is 0000 through 2359, with 0000 referring to midnight.

Required Fields: Fields that are required are noted by an asterisk (*) next to the question in OpenClinica. If a required field has not been answered, upon clicking ‘save,’ users will be prompted with a ‘discrepancy alert.’

The user must answer the missing question. Users will not be allowed to save the eCRF if data for a required field have not been provided.

Mark as Complete: An eCRF is not considered completed until the ‘Mark as complete’ option is selected on the last tab of each form. Users will not be able to select this option until all required fields (*) have been answered.

Skip Logic: Skip logic, also known as conditional branching, is used in the database to display different questions based on answers given to previous questions. For example, a question such as Was this subject enrolled in the study during a previous hospitalization?: if the response entered is Yes, the question Enter the OpenClinica Subject ID from the first enrollment will display. If the response entered is No, the question Enter the OpenClinica Subject ID will not display. In the view mode of OpenClinica, all questions will be displayed regardless of the conditional branching. However, in data entry mode only the questions that require data entry will display.

10.3 Study Events and Electronic Case Report Forms

This section provides a brief overview of how the Events and eCRFs are organized and for whom each eCRF must be completed:

Event Name	eCRF Name	eCRF Completion Requirements
Screening and CPR Event Information (repeating event)	Eligibility	Required for each screened CPR events in the C/PICU. If multiple CPR events occur for the same subject during the same hospitalization, an eligibility form is required for each screened CPR event.

Continued on next page

Table 10.5 (continued).

Event Name	eCRF Name	eCRF Completion Requirements
Screening and CPR Event Information (repeating event)	CPR Event Characteristics	Required for each eligible CPR event.
Screening and CPR Event Information (repeating event)	Post-CPR Event Care Variables	Required for each eligible CPR event with an outcome of ROSC or Transitioned to ECMO.
Screening and CPR Event Information (repeating event)	PRISM	Required for each eligible CPR event.
Screening and CPR Event Information (repeating event)	Vasoactive Inotropic Score	Required for each eligible CPR event.
Screening and CPR Event Information (repeating event)	Waveform and Defibrillation Data Upload Information	Required for each eligible CPR event.
Screening and CPR Event Information (repeating event)	CPR Later Found to be Unnecessary	Completed only if CPR is later determined to be unnecessary for an eligible CPR event.
Screening and CPR Event Information (repeating event)	<i>ETCO₂</i> Waveform Information	Completed only if <i>ETCO₂</i> waveforms are usable as determined by clinical review.
Subject History and Hospitalization Information	Demographics and Physical Measurements	Required once per Study Subject ID.
Subject History and Hospitalization Information	Baseline Functional Assessments	Required once per Study Subject ID.
Subject History and Hospitalization Information	Hospitalization Summary	Required once per Study Subject ID.
ICU Information (repeating event)	ICU Dates and Other Information	Required for each ICU admission per Study Subject ID.

Continued on next page

Table 10.5 (continued).

Event Name	eCRF Name	eCRF Completion Requirements
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10.4 eCRF Specific Data Entry Guidelines

10.4.1 Eligibility

This form is required to be completed for every patient screened for this study, whether eligible or ineligible, that meet a minimum of inclusion criteria.

- If a screened subject does not meet all inclusion criteria, do not enter this information into the database.
 - If a subject that does not meet inclusion criteria is entered into the database, *contact the Clinical Data Manager for assistance*
- If the subject meets inclusion criteria, but is ineligible because of meeting the exclusion criterion, proceed to enter the data on this form
- Eligible patients have all inclusion criteria answered "Yes" and all exclusion criteria answered "No"
- If this patient meets all inclusion criteria but is ineligible because he/she meets the exclusion criterion, data entry is complete for the subject.

10.4.2 CPR Event Characteristics

This form is required to be completed once per eligible CPR event. It documents CPR event characteristics pre-, during, and post-chest compressions. Data collected include, but are not limited to: start date/time of the CPR event, interventions in place, conditions present, first documented rhythm at CPR initiation, pharmacologic agents administered, end date/time of the CPR event, and the CPR event outcome.

10.4.3 Post-CPR Event Care Variables

This form is required to be completed once per eligible CPR event. It documents post-CPR event care vitals and labs twice over the first 24 hours

post-event. Data are required once up to 5 hours and 59 minutes post-event, and again between 6 and 24 hours post-event.

10.4.4 PRISM

This form is required to be completed once per eligible CPR event. It documents the worst physiologic values obtained during the following 4 hour timeframe: 6 hours prior to the CPR event through 2 hours prior to the CPR event. If the timeframe spans 2 calendar days, enter the first date for Date of Assessment.

10.4.5 Vasoactive Inotropic Score

This form is required to be completed once per eligible CPR event. It documents whether the subject was receiving vasoactive drips in the ICU exactly 2 hours prior to the CPR event, 6 hours post CPR event, and 24 hours post CPR event. If yes, the rate for each vasoactive medication are recorded.

If the subject was receiving Vasopressin drips at any of the time points listed above, enter the rate and select the units applicable to the site at which the data are collected.

10.4.6 Waveform and Defibrillation Data Upload Information

This form is expected to be completed once per eligible CPR event. It documents whether or not arterial waveform, *ETCO₂* waveform, and/or defibrillation data for the event are available, and if yes, whether or not these data were uploaded to the applicable ICU-RESUS Uploads eRoom folder for review.

10.4.7 CPR Later Found to be Unnecessary

This form is expected to be completed in the unlikely event that CPR was later determined to be unnecessary for an eligible CPR event.

10.4.8 *ETCO₂* Waveform Information

This form is intended to be completed on subjects that have usable end-tidal waveform data.

10.4.9 Demographics and Physical Measurements

This form is expected to be completed once for each enrolled subject.

10.4.10 Baseline Functional Assessments

This form is expected to be completed once for each enrolled subject. It is completed based on the subjects level of function prior to the event that brought her/him to the hospital. It documents the last measurable PCPC and FSS prior to ICU Admission.

10.4.11 Hospitalization Summary

This form is expected to be completed once for each enrolled subject. It documents hospitalization summary information including whether or not the subject was enrolled in the study during a previous hospitalization, hospital admission and discharge dates/times, vital status at discharge, and limitations of care. If the subject required one or more EEGs within 72 hours post eligible CPR event or head imaging within 168 hours (one week) post eligible CPR event, reports for each EEG and/or head image are uploaded on this form. Hospital discharge PCPC and FSS data are also collected.

10.4.12 ICU Dates and Other Information

This form is expected to be completed for each ICU admission for the enrolled subject. It documents ICU admission and discharge dates/times, the ICU illness category, and previous in-hospital cardiac arrest information.

10.5 Survey Data Entry

This section provides a brief overview of each REDCap survey available for completion. These surveys are completed at specified time points by

designated site personnel once the sites transition period begins through study completion.

Survey	Time Point Completed	Completed by
RESUS POC Bedside CPR Training (i.e., Rolling Refreshers)	After each individual Rolling Refresher training	Site Champion or RC
RESUS QI Initiatives	Quarterly	Site Champions
RESUS Monthly Debriefs	After each Debriefing session	Debriefing Facilitator

Part IV

Appendices

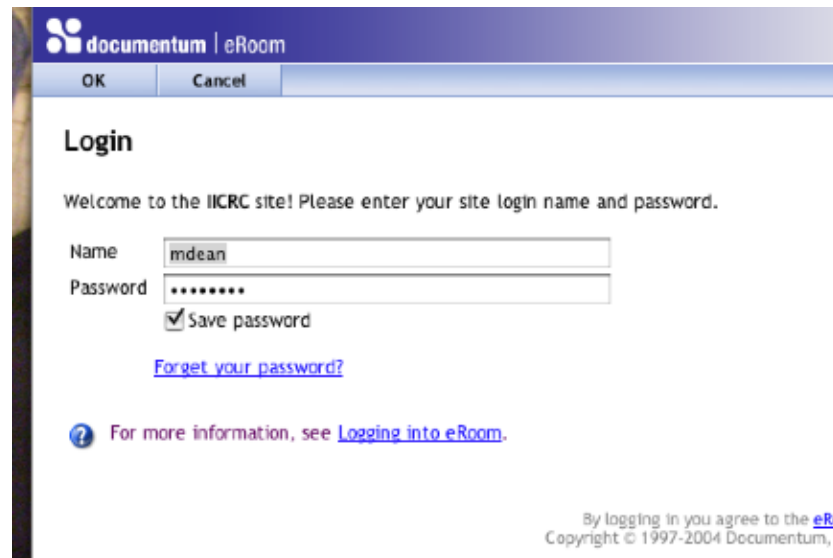
Appendix A

Use of eRoomTM in CPCCRN

Contents

A.1	How to Connect	118
A.2	CPCCRN Steering Committee eRoom	119
A.3	Common Items	122
A.3.1	Folders and Files	122
A.3.2	Web Links	122
A.3.3	Polls	124
A.3.4	Databases	124
A.4	How to Use Versioning	126
A.5	eRoomTM Backup	127

The DCC uses a commercial software product produced by Documentum called eRoomTM to support collaboration among users across the United States, and we currently have approximately 500 users. The system is designed as an electronic, virtual office facility, and can be reached from anywhere in the world via the Internet, using a simple Internet browser. The purpose of this appendix is to refresh CPCCRN investigators with the use of the system.

Figure A.1: Logging in to eRoomTM

A.1 How to Connect

The eRoomTM facility is maintained on an SSL (secure socket layer) server at the University of Utah. All this means to you is that instead of typing [http://](#) at the beginning of the address that your browser will try to contact, you must type [https://](#) (note the s). All communications between your browser and the SSL server are securely encrypted.

The URL or Internet address of our eRoomTM system is <https://www.nedarcssl.org/eroom> and you may access this with Microsoft Internet Explorer, Netscape, Mozilla, Safari, Firefox, or almost any browser available to you. You will see something similar to Figure A.1.

Your user name has been provided to you, but in case you forgot it, it is your first name initial and last name, typed all in lowercase, typed as one word. In the example figure, Mike Dean's user name is mdean. If you have never logged into the eRoomTM facility before, your initial password is pediatrics.

On a Windows machine, you will be asked if you wish to install a plug-in to help you work with eRoomTM. This plug-in is not relevant to Macintosh users. If you are offered this option, we recommend that you accept the plug-in. The most important added functionality is that you can drag and

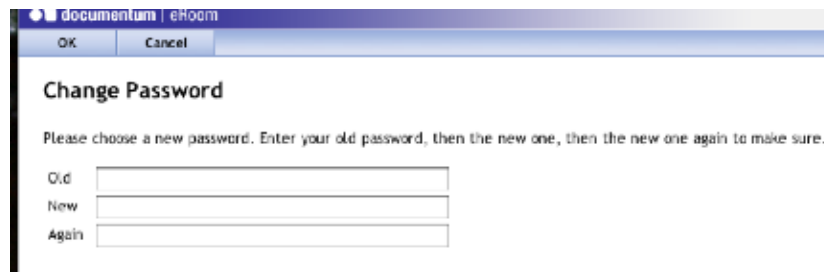


Figure A.2: Changing your password.

drop files between your Windows desktop and the eRoomTM pages. If you prefer not to install the plug-in, or if you are located at a computer on which you are not allowed to install software, then indicate that you do not wish to use the plug-in.

If you have never logged in previously or if your password has been reset, you will be asked to change your password. The dialog for doing this is shown in Figure A.2.

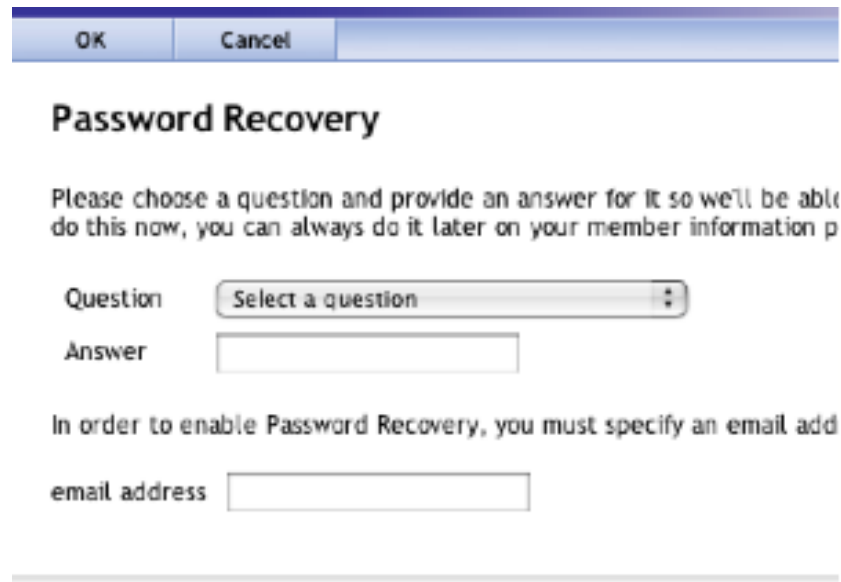
You will have an opportunity to enter a password recovery question, which is a personal question so you can verify your identity to the system and reset your own password (see Figure A.3 on the next page).

After you type your name and password, press the return or enter key, and you will go to a page called “My eRooms”, resembling Figure A.4 on the following page. Only the eRooms for which you are a member will be listed on the page.

You can check any eRooms that are listed and then these will be added to your “Active eRooms” section toward the top of the screen. If you prefer, you can just click on the name of the eRoom (for example, “CPCCRN Steering Committee and Staff”) and you will be taken directly to the eRoom. When you are a member of many eRooms, it is convenient to set up your “Active eRooms” to simplify finding the eRoom you wish to use. For example, an administrator might have more than 200 eRooms listed. The top of his page might look like the screen shown in Figure A.5 on page 121.

A.2 CPCCRN Steering Committee eRoom

The top section of a network Steering Committee eRoom looked something like Figure A.6 on page 123 in the late spring, 2005. The section on the left



OK Cancel

Password Recovery

Please choose a question and provide an answer for it so we'll be able to do this now, you can always do it later on your member information page

Question

Answer

In order to enable Password Recovery, you must specify an email address

email address

Figure A.3: Recovering your password after you forgot it.



documentum | eRoom

My eRooms

My eRooms

search this site create an eRoom my member info organize

Active eRooms

You have not yet any eRooms on your Active eRooms list.

active	eRoom	description
☐	CPCCRN Steering Committee and Staff	Steering committee and all faculty and staff associated with the NIH-funded CPCCRN. Used to provide overall discussion and information about the network to all CPCCRN individuals.

Figure A.4: Listing of your active eRooms.

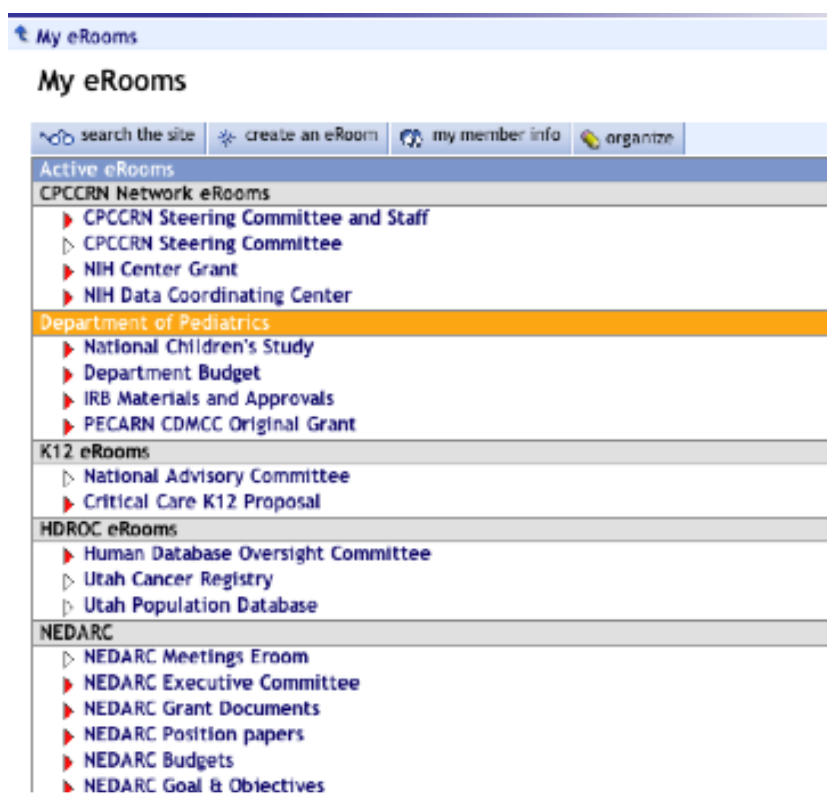


Figure A.5: Listing of active eRooms for busy user.

side is an outline-like navigation view, the bulky section is the icon view of the eRoom, and the red text is material that you have not previously seen.

Red arrows or red text, as shown in Figure A.6 on the next page, indicate that you personally have not opened or seen the material. This is convenient because if you visit a busy eRoom, you would like to know what is new for you. If you click on the red arrow on the top right of the screen, this will take you to the first unread item.

If you want to indicate that you have seen everything without reading it, you may click on the “mark read” button that is below all the icons. This is convenient if you are starting out fresh but want to keep up with all new items henceforth.

A.3 Common Items

Your use of eRoomTM will increase with time and experience, but several items are worthy of description.

A.3.1 Folders and Files

There are a number of folders, which contain other things. The meeting folder will contain information about Steering Committee meetings. There was a folder about the pertussis project, and it contained additional documents, as shown in Figure A.7 on page 124. Note that this folder does not exist today, because the project has been moved to its own eRoom.

You see the pertussis proposal (Pertussis.pdf) in the middle of the documents shown in Figure A.7 on page 124, as well as references that were included as background to the project. If you click on such PDF documents and have Adobe Acrobat or Reader on your computer, then the PDF documents will automatically open.

A.3.2 Web Links

Anything that looks like a green globe is a Web link. In Figure A.6, you will see several links to the MCHB main page, NEDARC, and the GCP training website.

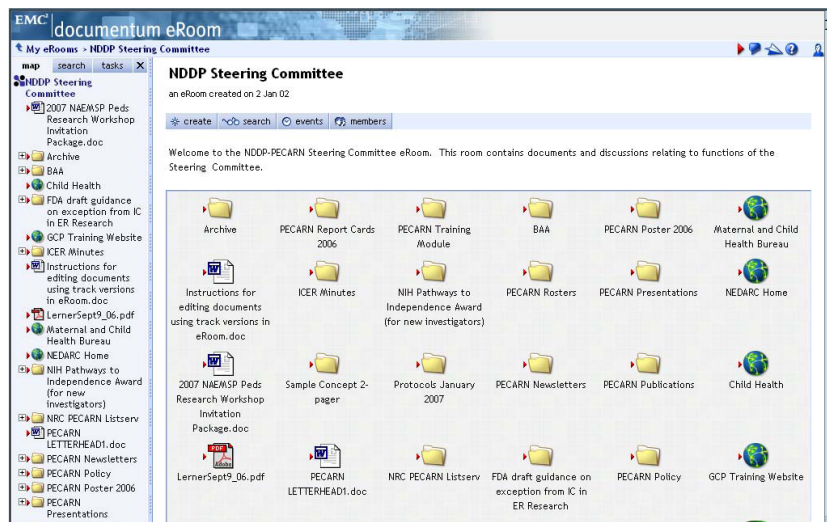


Figure A.6: Sample Network Steering Committee eRoom, circa July 2007.

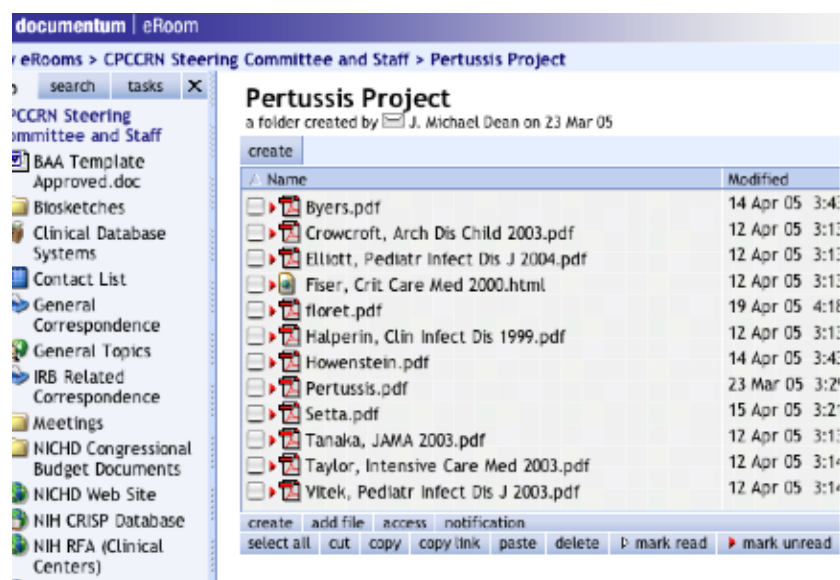


Figure A.7: Old pertussis folder in Steering Committee eRoom, May 2005.

A.3.3 Polls

These icons look like voting boxes and are used to get opinions or answers from members of the eRoom. This is very convenient for avoiding large numbers of phone calls and email traffic. The two polls that are visible in Figure A.6 concerned the future dates of steering committee meetings and some brief questions about your computer systems.

A.3.4 Example Database - the Contact List

There is a blue grid-like icon called Contact List (in the upper right of Figure A.6 on the preceding page). The DCC entered data about your contact information in this database, and CPCCRN investigators and research coordinators have maintained their own information. You may edit your entries into this database. Data coordinating center staff will try to keep this up to date, but we stress that you should make an effort to keep your own information up to date.

The contact list can be rearranged in a variety of ways. You might look at the database by name (Figure A.8 on the next page), organization (Figure A.9 on the facing page), or role in the CPCCRN (Figure A.10).

Maintain the contact information for all the current mem

Group by (none)		
	Name	Email
	Dean, J. Michael	mike.dean@hsc.uta
	Anand, K.S. (Sunny)	anandsunny@uams.
	Dalrymple, Robin	dalrymplerobin@u
	Hefley, Glenda	hefleyglenda@uam
	Marron, Sharon	sharon.marron@hsc
	Zuspan, Sally Jo	sally.zuspan@hsc.u
	Holubkov, Richard	rholubkov@hrc.uta

Figure A.8: Showing contact information by name.

new entry

Maintain the contact information for all the current

	Group by Organization			
+	Name	Email	Role	Org
+	Arkansas Children's Hospital 3			
+	Children's Hospital Los Angeles 3			
+	Children's Hospital of Michigan 4			
+	Children's National Medical Center 3			
+	National Institutes of Health (NICHD) 3			
+	Seattle Children's Hospital 3			
+	University of California Los Angeles 1			
+	University of Pittsburgh 1			
+	University of Utah School of Medicine 16			
+	University of Virginia 2			
new entry notification export import				
select all cut copy copy link paste delete ▶ mark				

Figure A.9: Showing contact information by organization.

new entry

Maintain the contact information for all the current members of the CPCCRN network

Group by	Role				
Name	Email	Role	Organization		
Principal Investigator 7					
Co-Investigator 6					
Research Nurse 5					
Hefley, Glenda	hefleyglenda@uams.edu	Research Nurse	Arkansas Ch		
Frey, Maureen	mofrey@wowway.com	Research Nurse	Children's H		
Reardon, Jean	jreardon@cnmc.org	Research Nurse	Children's H		
Auw, Lori	lauw@chla.usc.edu	Research Nurse	Children's H		
York, Andrea	andrea.york@comcast.net	Research Nurse	Seattle Chil		
Data Abstractor 1					
Project Scientist and Program Director 1					
NICHD Staff 2					
Network Chairman 1					
Program Manager 2					
Site Monitor 1					
Biostatistician 5					
IT Manager 1					
Administrative Staff 10					

new entry | notification | export | import
select all | cut | copy | copy link | paste | delete | mark read | mark unread

Figure A.10: Showing contact information by role in network.

A.4 How to Use Versioning

Finally, a few words about how documents can be produced in a collaborative environment. First, you may place a new document into the eRoom by dragging it directly into the eRoom. You may create folders or other items by clicking on the create button inside the eRoom, and you may organize documents, etc.

When you place a document in the eRoom, you are the owner. You can set several important things by right-clicking on the item. This will result in a drop down menu. The drop down has an item called “track versions” which is checked in Figure A.11. This means that eRoomTM will save all versions of the document. You should ALWAYS set this on, because then eRoomTM will take care of saving every version. You may also set the “access control” which determines who can open, edit, or see your document. Finally, if you wish to edit a document in eRoomTM, you need to use this right-click method and select “edit”. When you simply left-click on an item in eRoomTM, which is the normal mouse click, then the default is that you can view the document but your are not in an editing mode.

Consider the workflow that might ensue with a research manuscript. A draft document would be placed in the eRoom by the original author, who

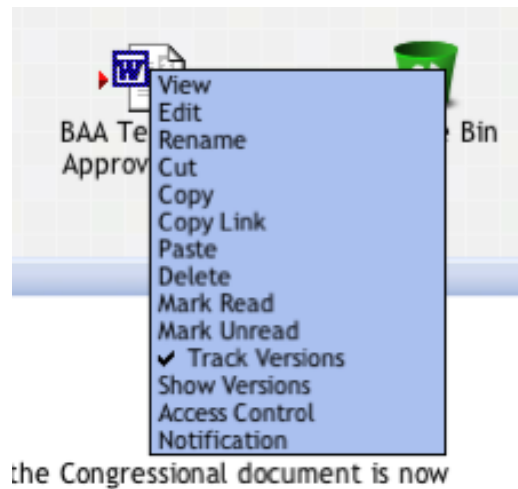


Figure A.11: Right clicking the mouse to turn on version tracking.

could set it to be visible to everyone in our eRoom, but only editable by one or two people. When the editors want to work on the paper, they select the edit drop down, and the paper will open on their computer automatically. After working on the paper, they save it and it will be placed back in eRoom. They will be asked to provide some version information. While a document is being edited, it is locked and no other people can simultaneously edit it. However, other people CAN read the version on the eRoom.

The real working version should always be stored on eRoomTM. This eliminates any confusion about who has the most recent version on which computer. By doing this, you can reach any of your work from any computer in the world. In addition you take advantage of our back up facilities.

A.5 eRoomTM Backup

The eRoomTM is backed up at the University of Utah every hour during the week, and on a weekly basis, a complete backup is stored deep in a mountain that is capable presumably of sustaining a nuclear blast. For this reason, we urge all network participants to store their network-related work on eRoomTM at all times. There is no reason for you to keep private versions on your own computers, but this is a work habit that takes some time to develop.

Appendix B

Use of OpenClinica 3.1 Electronic Data Capture Software

Contents

B.1 What is OpenClinica?	130
B.2 Accessing OpenClinica Studies	130
B.3 Subjects and Events	132
B.4 Adding a New Subject	133
B.5 Scheduling an Event	133
B.6 Selecting and Entering Specific eCRFs	135
B.7 Viewing or Printing eCRFs	135
B.8 Entering Data in eCRFs	138
B.8.1 eCRF Header	138
B.8.2 Main Body of the eCRF	138
B.9 Discrepancy Alerts	140
B.10 Adding Rows to a Repeating Question Group . .	141
B.11 Uploads	142
B.12 Deletion of Study Subject IDs, Study Events and eCRFs	142
B.13 Getting Help	142

B.14 How to Log Out	143
B.15 What If the Internet Is Down?	143

B.1 What is OpenClinica?

OpenClinica is an open source electronic data capture (EDC) system developed by OpenClinica, LLC. OpenClinica is backed by an open source community comprising over 18,000 registered individuals from hundreds of leading industry, academic, and government research institutions in over 100 countries around the world. The University of Utah Data Coordinating Center (DCC) is using this application to support clinical research studies that are conducted within the Collaborative Pediatric Critical Care Research Network (CPCCRN).

B.2 Accessing OpenClinica Studies

OpenClinica is a web-based software system, and is accessed from either Internet Explorer 5.5+ or Mozilla Firefox 1.0+ on Windows or Macintosh based computers. When the user types in the URL for OpenClinica, it will start with ‘https: //’ rather than ‘http: //’ because it uses secure socket layer (SSL) encryption. User accounts are administered through a single sign-on system called Active Directory. This system allows a single account to access multiple systems utilized by the DCC. Password changes or resets are managed via Active Directory. The actual URL for OpenClinica, as well as account names and passwords, are provided separately from this Manual when individual user accounts are configured.

The log-on page has a place to enter the username and password (See Figure [B.1 on the next page](#)). Once a username and password are entered, click the “Login” button or “Enter” key to access the system.

Logging in will lead to the homepage navigation screen (See Figure [B.2 on page 132](#)). The homepage displays the study currently logged into and the user’s role within that study. By default, the last study a user was logged into will be the study that opens upon re-entry in to the system. If users are participating in more than one study, there is an option to “Change Study/Site” at the top middle of the screen. Selecting the “Change Study/Site”



The image shows the OpenClinica Enterprise login and news page. The header features the OpenClinica logo in blue and the word ENTERPRISE in large, grey, spaced-out capital letters. Below the header, there are two main sections: a login form on the left and a news section on the right.

Login

User Name

Password

[Login](#) [Forgot Password?](#)

News

- ▶ 04/26 - New OpenClinica Developer Release: Revamped Print Module - A new developer release is available for ...
- ▶ 04/23 - OpenClinica to present at DIA China Annual Meeting - There are numerous opportunities to learn about ...
- ▶ 04/09 - Importing OpenClinica Data Into R - R is a powerful open source statistical software ...
- ▶ 04/02 - Using Patient-centered Technology to Improve Recruitment and Retention - Sponsors of clinical research must increasingly ...

[More...](#)

Figure B.1: Logging into OpenClinica

OpenClinica ENTERPRISE TOPICC Phase II : TOPICCII - Utah Data Coord... (TOPICCb_UDCC) | Change Study/Site apetersonRC (Clinical Research Coordinator) en | Log Out

Home | Subject Matrix | Add Subject | Notes & Discrepancies | Tasks | Report Issue | Support | Study Subject ID | Go

Alerts & Messages | **Instructions** | **Other Info**

Study: TOPICC Phase II

Site: TOPICCII - Utah Data Coordinating Center

Start Date: N/A

End Date: 05-Dec-2011

PI: J. Michael Dean, MD, MBA

Protocol Verification/IRB Approval Date:

Welcome to TOPICC Phase II

Notes & Discrepancies Assigned to Me: 0

15 | Show More | Select An Event | Add New Subject

Study Subject ID	Phase II Hospital Admission	Phase II PICU Course	Phase II Hospital Discharge	Phase II PICU Limitations/Withdrawal of Care	Ph
107744	✓	✓	✓	✓	
107799	✓	✓	✓	✓	
107818	✓	✗	✓	✓	
107823	✗	✗	✗	✗	
108755	✗	✗	✗	✗	
109311	✗	✗	✗	✗	
112988	✗	✗	✗	✗	

Results 1 - 7 of 7.

Figure B.2: Homepage navigation screen

option will navigate the system to another screen where users can click a radio button to switch to a different site and/or study.

The homepage screen contains an information column down the left side of the page. This information column is displayed on all pages in which there is no data entry. The information column displays the study a user is logged in to, the site for which a user is viewing/entering data, the start and end date of the study, the clinical site principal investigator, and the protocol verification / IRB approval date for the study.

B.3 Subjects and Events

Also displayed on the homepage navigation screen is the “Subject Matrix.” This table provides an event completion status summary of subjects enrolled at a clinical site and listed by study subject ID (automatically generated by OpenClinica). Users only see subjects who have been enrolled at their own site. The option to view 15, 25 or 50 subjects within a screen is available from the drop down menu located above the “Study Subject ID” field.

The column(s) in the subject matrix are the events defined for the study. The number of columns displayed depends on the number of events in the study. The icon just below the event name displays the status of the event for each patient listed in the table. There are also a number of available filtering options: by Study Event, by Study Subject ID and by status of a given Study

Event.

An icon key is provided on the left margin of all pages that use the icons within OpenClinica.

B.4 Adding a New Subject

OpenClinica offers a few options to create a study subject ID. The following options do the same thing but vary slightly with the number of fields to enter within the screens:

1. Two “Add Subject” links are available at the navigation bar. The first, located on the bar, allows users to save and assign one study event or add multiple study subject IDs at one time. The fields included in this view are Study Subject ID, Secondary ID, Date of Enrollment and Sex. The second link is located under the “Tasks” menu. The fields in this view are identical to the “Add Subject” link.
2. An “Add New Subject” link is also located at the top of the Subject Matrix table, to the right of the “Select An Event” drop-down menu. There are additional questions in this view: Study Event, Location and Start Date. Users do not have the option to schedule multiple study events or create additional study subject IDs from this screen.

Refer to Figure [B.3 on the next page](#) for the “Add Subject” link that is located on the top navigation bar. The fields on the “Add Subject” screen are defined by the specific requirements of the study. Please refer to each study’s specific data entry guidelines for instructions on how to complete the “Add Subject” screen.

B.5 Scheduling an Event

In order to enter data into the electronic case report form (eCRF) for the study, the event that contains the eCRF a user wishes to enter must be scheduled. There are several ways to schedule an event. The most direct is from the “Add Subject” screen (see Figure [B.3 on the following page](#)), where users may click the “Save and Assign Study Event” box to navigate to the “Schedule Study Event” screen. Another option from the Subject Matrix is

Utah Data Coordinating Center: Add Subject ?

* indicates required field.

Study Subject ID:	AUTO_ID	*
Person ID:		
Secondary ID		
Date of Enrollment for Study: The CAMMP Study	25-Mar-2010	 
Sex:	-Select-	 

[Save and Assign Study Event](#)[Save and Add Next Subject](#)[Save and Finish](#)[Cancel](#)

Figure B.3: “Add Subject” screen

to click on the notepad icon () directly below the name of the event for the subject data entry needs to be completed for. Either navigation will bring users to the “Schedule Study Event for (*Study Subject ID*)” screen (See Figure B.4 on the next page).

From this screen, select the “Study Event Definition” from the dropdown box to the right of the field. All the events available in the study will be listed in the selection options. Unless otherwise noted for a particular study, all of the remaining necessary information to schedule the event will be pre-populated. The only action users must complete is clicking the “Proceed to Enter Data” button, in the middle left of the screen. *Please note: some study specific requirements may require users to change the “Start Date / Time” field.*

B.6 Selecting and Entering Specific eCRFs

After the “Proceed to Enter Data” button has been selected, users will be navigated to the “Enter or Validate Data for eCRFs In (*Event Name*)” (See Figure B.5 on page 137). This page displays the event data in the top box and an Edit Study Event icon () can be clicked to edit the event status, if necessary. The bottom box displays the eCRFs available for data entry for the event that has been scheduled. To the right of the box an “Actions” column with 3 options for each eCRF is displayed. To start entering data into the eCRF, click the icon that looks like a notepad with a pencil () and proceed to enter data. *Please be sure to save data as each section is completed or the data entered will be lost.*

B.7 Viewing or Printing eCRFs

From the “Enter or Validate Data for CRFs In (*Event Name*)” screen (See Figure B.5 on page 137), users may also view or print an eCRF by clicking on the appropriate icon in the “Actions” column. Select the magnifying glass icon () the middle option in the “Actions” column, next to the eCRF users wish to view the data for. Select the print icon () the last option in the “Actions” column, next to the eCRF users wish to print data for.

Schedule Study Event for 1048 ?

* indicates required field.

Study Subject ID: **1048**

Study Event Definition: Patient Demographics & History (non-repeatin ▼ *)

Location: Salt Lake City * 

Start Date/Time: 17-Mar-2010  ▼ : ▼ (DD-MMM-YYYY HH:MM) * 

End Date/Time: ▼  ▼ : ▼ (DD-MMM-YYYY HH:MM) 

Leave this field blank if the end date/time is not applicable.

☐ Schedule Another Event: (optional)

☐ Schedule Another Event: (optional)

☐ Schedule Another Event: (optional)

☐ Schedule Another Event: (optional)

Proceed to Enter Data **Cancel**

Figure B.4: “Schedule Study Event for (Study Subject ID)” screen

Enter or Validate Data for CRFs in Patient Demographics & History

Edit Study Event

Study Subject ID	6589
Study Event	Patient Demographics & History
Location	Salt Lake City
Study Subject OID	SS_6589
Start Date	28-Mar-2010
End Date/Time	
Subject Event Status	scheduled
Last Updated by	0

CRFs in this Study Event:

CRF Name	Version	Status	Initial Data Entry	Double Data Entry	Actions
CAMIMPS Demographics	v1.0				
CAMIMPS History	v1.0				

View this Subject's Record

Exit

Figure B.5: “Enter or Validate Data for eCRFs in (Event Name)”

B.8 Entering Data in eCRFs

OpenClinica has a relatively consistent interface for the eCRFs. At the top of each eCRF is a box containing header information. Below this box is the main body of the eCRF, which can consist of one or many sections (See Figure B.6 on the facing page) each section of the form is represented by a tab.

B.8.1 eCRF Header

At the top of every eCRF, the header displays the current eCRF being worked on, a discrepancy notes (query) section which will show users the number of new, updated, resolved, proposed, closed, and not applicable queries for this eCRF. Discrepancy notes are managed differently for each study; please refer to study specific guidelines for specifications. The study subject ID, study/site, and event are also displayed in the eCRF header. If the study requires the name of the person doing the data entry and the date for which the event was created, the Interviewer Name and Interviewer Date columns will be displayed. All of the information in the eCRF header has been populated from either the study subject or event information previously entered on other screens. The eCRF header is not editable on the data entry screens. This information is always seen in the header section so that the person entering data can be certain they are entering data for the right patient.

B.8.2 Main Body of the eCRF

The main body of the eCRF contains questions broken out by each defined section. eCRFs may have one or more sections. Each section is displayed in there defined order by tabs from left to right. If an eCRF has more than three sections, only three tabs will be displayed across the top at a time. Each section has a label which is shown on the tab and a title which is shown at the top of the page for each section. In Figure B.6 on the next page, notice that there are three tabs displayed followed by a “Select to Jump” drop down box. This box allows navigation from one section to any other section on the form without first needing it displayed as a tab on top.

The forms display one section (tab) at a time and NOT a complete eCRF. Displaying the forms in this manner allows users to save data entered one section at a time. To continue to the next section of an eCRF, select “Save”. If a user happens to select exit prior to completing data entry, a pop-up

TOPICC Phase II Hospital Admission Information v1.0

107823

- CRF Header Info	
Event:	Phase II Hospital Admission (09-May-2013)
Study:	TOPICC Phase II
Site:	TOPICCI - Utah Data Coordinating Center
Interviewer Name: *	apetersonRC
Sex:	
Age At Enrollment:	
Interview Date: *	09-May-2013 
Discrepancy Notes on this CRF:	
New	Updated
Resolution Proposed	Closed
Not Applicable	
0	0
0	0
0	0
0	0
0	0

◀ **Demog (0/8)** **History (0/10)** **Baselin... (0/10)** ▶ -- Select to Jump -- ▼

Title: Patient Demographics

Page: **Save** **Exit** 

Was this patient already enrolled in the TOPICC study during a previous hospitalization?

(select one) ▼ If yes, enter the EDC Subject ID for the first enrollment:

Date of birth: * (DD-MMM-YYYY) 

Sex: ☐ Male ☐ Female *

Ethnicity: ☐ Hispanic or Latino * ☐ Not Hispanic or Latino ☐ Unknown or Not Reported

Race: ☐ American Indian or Alaska Native * ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Unknown or Not Reported

(select all that apply)

Residential Zip Code:

Please select the most appropriate primary payer type:

(select one) ▼

[Return to top](#) **Save** **Exit** 

Figure B.6: Anatomy of OpenClinica

warning will display stating “You have unsaved data. Are you sure you want to exit without saving?”

As noted previously, only three tabs are displayed at once on an eCRF, but an eCRF can have more than three sections. Please take note of the small blue arrow between the last tab and the “Select to Jump” box which also allows navigation between different sections.

As data are entered in each section and “Save” is clicked, the tabs will automatically advance. Once the last tab is reached on the eCRF, a “Mark CRF Complete” checkbox will be displayed next to the “Save” button at both the top and bottom of the screen. Users will also know they have reached the end of the eCRF because upon hitting “save,” the screen will not advance. The “Mark CRF Complete” checkbox should be selected when data entry on the form has been completed for all sections.

OpenClinica employs different options for answering the data collection questions such as: single-select radio buttons or drop down lists, multi-select drop down lists or checkboxes, and open text fields. The open text fields can be programmed to accept only the type of data the question is asking for. For example, if the question is asking to provide a time value in the 24-hour clock, only data entered in the 24-hour clock format will be accepted. Otherwise users will receive a discrepancy alert (pop-up warning box) describing the type of data that are acceptable to enter in the open text field.

Skip logic, also known as conditional branching, is used in OpenClinica to display different questions based on answers given to previous questions. For example, the question asks “Was this patient enrolled in the study during a previous hospitalization?” If the reply is “yes,” the question “Enter the OpenClinica Subject ID from the first enrollment” will display. If the reply is “no,” the question to provide the OpenClinica Subject ID will not display. In the view mode of OpenClinica, all questions will be displayed regardless of the conditional branching. However, in data entry mode only the questions that require data entry will be available for data entry.

B.9 Discrepancy Alerts

Fields that are required are noted by an asterisk (*) next to the item name in OpenClinica. If a required field has not been answered, upon clicking save, users will be prompted with a discrepancy alert. Users must answer the missing question. If data for a required field has not been provided, the

system will not allow the eCRF to be saved.

Dates must be entered in DD-MMM-YYYY format, with MMM being the 3 letter English month abbreviation with only the first letter capitalized, i.e., Jan, Feb, Mar, Apr, May, etc. Dates not entered in this format cannot be saved. Using the pop-up calendar function will ensure dates are correctly formatted.

Times must be entered in HHMM format using the 24 hour clock. The valid range for times is 0000 through 2359, with 0000 referring to midnight.

Another type of discrepancy alert is a warning when a value is out of range. A discrepancy alert will appear as with the required, date, and time fields; however, if the data entered are correct, hitting the Save button again will advance users to the next tab of the eCRF. This type of discrepancy alert does not have to be corrected in order to save data.

There are issue(s) with your submission. The data has NOT been saved. See below for details.

- [The input you provided is not a valid date in DD-MMM-YYYY format.]
- [Missing data in a required field.]
- [Enter time in format HHMM on 24 hour clock.]

Study 5... (0/7) -- Select to Jump --

Title: Study Summary

Instructions: This form is to be completed at hospital discharge OR 12 hours after last IV opioid administration.

Page: ☐ Mark CRF Complete **Save** **Exit**

Record date/time of Hospital Discharge:

Date: ! 01-01-2010 (DD-MMM-YYYY) Time: ! 2400 (HHMM)

Record date/time of FIRST IV opioid administration received by patient:

Date: ! (DD-MMM-YYYY) Time: (HHMM)

Figure B.7: Discrepancy Alerts

B.10 Adding Rows to a Repeating Question Group

eCRFs containing repeating question groups (RQG) are a common feature. They are often seen in instances of multiple laboratory collections and in logs such as Adverse Events and Concomitant Medications. To add a row within the repeating group, click on the “ADD” button. Users are not allowed to delete a row from a RQG once the form has been saved. In cases when a

row of data must be removed, manually delete each response. If one of the questions contains a choice set, de-select the response by selecting the default value, which is typically named “Select one.”

B.11 Uploads

Some studies will require reports to be uploaded within an eCRF. Before uploading any report, ensure that all subject identifiers are removed and the Study Subject ID is clearly written on at least the first page of the report. In addition, if the file is required to be converted to a specific format, instructions for how to do this can be located in the data management chapter of this MOO. To upload a report, click on the “Click to upload file” button. A pop-up window will appear, containing a browse field to select the file to be uploaded. Once the file is selected, click the “Upload File” button and then close the window. Note that only one upload can be saved at a time.

After the report has been uploaded and the eCRF has been saved, two new buttons will appear giving the option to “Replace” or “Remove” the upload.

B.12 Deletion of Study Subject IDs, Study Events and eCRFs

If an eCRF is mistakenly created, contact the Lead Clinical Data Manager and make a request to delete the eCRF from the database. The same also applies to Study Subject IDs and Study Events, contact the Lead Clinical Data Manager to remove these from the database. A reason for each removal must be provided. Users do not have the capability to delete eCRFs or remove Study Events or Subject IDs.

B.13 Getting Help

For study related questions regarding data entry for an eCRF, please contact the study Lead Clinical Data Manager at the DCC.

B.14 How to Log Out

It is important to log out of the system when finished by selecting the “Log Out” button from the top right hand corner of any non-data entry screen. If a user forgets to log out, or if there is no activity on the system for 30 minutes, the session will automatically disconnect. If the session is disconnected the system will direct users back to the main log in screen.

B.15 What If the Internet Is Down?

OpenClinica requires an Internet connection. If the clinical site or the Utah DCC loses connectivity, OpenClinica will not be available. While this is rare, it does occur occasionally. In the event that OpenClinica is not accessible, clinical site staff should use paper forms until connectivity is re-established.

Index

- ETCO₂* Waveform Information, [89](#)
- National Heart, Lung, and Blood Institute (NHLBI)
 - inspection by, [48](#)
- Clinical Center
 - available documents, [45](#)
 - site inspections, [47](#)
 - site monitoring visits, [44](#)
- Baseline FSS and PCPC, [91](#)
- Collaborative Pediatric Critical Care Research Network (CPCCRN)
 - background, [3](#)
 - Data Coordinating Center, [3](#)
 - purpose, [3](#)
- CPCCRN, *see* Collaborative Pediatric Critical Care Research Network
- Data Coordinating Center (DCC)
 - role, [4](#)
- Data Management, [107](#)
- DCC, *see* Data Coordinating Center
- Death Data, [93](#)
- Definition of CPR Event, [77](#)
- Demographics, [91](#)
- Discharge FSS and PCPC, [93](#)
- dsmb, [51](#)
- Eligibility, [78](#)
- eRoom, [117](#)
 - backup, [127](#)
 - collaborative workflow, [126](#)
 - connecting, [118](#)
 - contacts database, [124](#)
 - databases, [124](#)
 - databases, sorting by fields, [124](#)
 - folders and files, [122](#)
 - logging in, [118](#)
 - password, [119](#)
 - password, changing, [119](#)
 - polls, [124](#)
 - Steering Committee eRoom, [119](#)
 - URL for CPCCRN, [118](#)
 - URL for PECARN, [118](#)
 - usable browsers, [118](#)
 - user name, [118](#)
 - versioning documents, [126](#)
 - Web links, [122](#)
- Essential Documents Binder, [45](#)
- Event Characteristics, [81](#)
- FDA, *see* Food and Drug Administration
- Food and Drug Administration (FDA), [43](#), [46](#), [47](#), [66](#)
- GCP, *see* Good Clinical Practice
- Good Clinical Practice (GCP), [43](#)
 - DCC activities, [44](#)
 - data archival requirements, [46](#)
 - definition, [43](#)
 - Essential Documents Binder, [45](#)
 - site monitoring, [44](#)
 - University of Utah policy, [43](#)
- Health Insurance Portability and Accountability Act (HIPAA), [47](#)
- Hospitalization Information, [92](#)
- ICH, *see* International Committee on Harmonization
- ICU Information, [93](#)
- Informed consent, [63](#)
 - forms, [62](#)

- translation, 62
- IRB approval, 62
- Institutional Review Board (IRB), 46, 61
 - DCC reminders, 5
 - DCC required documents, 5
 - amendment documentation, 64
 - amendments to protocol, 64
 - annual renewal of approval, 67
 - annual review, 5
 - approved informed consent, 62
 - communications, 66
 - date of approval, 64
 - denial of approval, 62
 - documentation, 61
 - expiration of approval, 64
 - failure to provide DCC documentation, 5
 - investigator responsibility, 5
 - meeting minutes, 61
 - Principal Investigator responsibilities, 46
 - renewal dates, 63
 - suspension of study, 68
- International Committee on Harmonization (ICH), 43
- Investigator responsibility, 65
 - study oversight, 65
 - adequate time, 66
 - adherence to GCP, 66
 - communication with IRB, 66
 - delegation to staff, 69
 - delegation to staff, documentation, 70
 - protocol compliance, 67
 - regulatory documents, 66
 - reporting adverse events, 66
 - staff training, 69
- IRB, *see* Institutional Review Board
- Manual of Operations (MOO)
 - purpose, 4
 - vs Study Protocol, 4
- MOO, *see* Manual of Operations
- National Institute for Child Health and Human Development (NICHD), 3
 - approval of site monitoring, 45
- NICHD, *see* National Institute for Child Health and Human Development
- OpenClinica, 130
- Post-CPR Event Hemodynamic Variables, 89
- PRISM & Glasgow Coma Scale, 90
- SAE, *see* Serious Adverse Events
- Screening, 77
- Site inspections, 47
- Site Monitoring
 - visits, 53
- Site monitoring, 44
- Staff training, 69
- Study termination or suspension, 68
- Study Work Flow, 76
- Waiver of Consent, 79
- Waveform Data, 80

