Bleeding and Thrombosis During ECMO (BATE)
CPCCRN Protocol Number 048

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

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This protocol is CPCCRN Protocol Number 048, and the lead CPCCRN investigator for this protocol is Heidi J. Dalton, M.D., Phoenix Children's Hospital.

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PROTOCOL TITLE:

Bleeding and Thrombosis During ECMO

Short Title: BATE
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Lead Investigator and Author:
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Phoenix Children's Hospital

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Bleeding and thrombosis represent major adverse events during extracorporeal life support. The most widely available form of extracorporeal life support in children is extracorporeal membrane oxygenation (ECMO). Complications resulting from these events can lead to death or need for long term rehabilitation support. Despite the increasing use of extracorporeal support and new technology which makes it simpler and potentially safer to apply, little scientific information regarding the predictors of bleeding or thrombosis exist. While anticoagulation during ECMO is required to prevent clotting within the ECMO circuit, the optimal means to administer anticoagulation, monitor and treat observed abnormalities is not well understood nor standardized. This project will seek to describe the incidence of bleeding and thrombosis in ECMO patients at CPCCRN sites, describe current anticoagulation monitoring practices and seek evidence of association between bleeding and thrombotic complications, laboratory coagulation measurements, patient characteristics, ECMO circuitry and adherence to center-specific ECMO management protocols. The ultimate goal of this research is to eliminate bleeding and thrombotic complications during ECMO and improve outcome for these patients.

1 Study Summary

1.1 Hypotheses

The hypotheses of this prospective, observational cohort study are that bleeding and thrombotic complications are:

1. frequent, and negatively impact survival of children receiving ECMO;
2. associated with abnormal laboratory coagulation measurements;
3. associated with different ECMO circuitry; and
4. possibly associated with lack of adherence to center-specific protocols concerning monitoring of anticoagulation and transfusion.

1.2 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Measure the incidence of bleeding and thrombotic complications in a prospective cohort of children receiving ECMO.

Specific Aim 2. Quantitatively and qualitatively describe monitoring practices for anticoagulation.

Specific Aim 3. Seek evidence of association between bleeding and thrombotic complications, laboratory coagulation measurements, patient characteristics, ECMO circuitry, and adherence to center-specific ECMO management protocols.

1.3 Subject Eligibility, Accrual and Study Duration

Inclusion criteria:
Patients will be eligible for enrollment if they:

- are between the ages of 0 days to <19 years of age; AND
- are admitted to a Pediatric, Cardiac, or Neonatal ICU of a CPCCRN network site; AND
- have received ECMO at time of or during the admission.

Exclusion Criteria:
Patients are ineligible to be enrolled as study subjects if the following is true:

- have been enrolled in this study previously.

Some subjects will have multiple ICU admissions; only the first admission associated with ECMO will be included. ICU admissions prior to the ICU admission during which the patient receives ECMO are not to be included. Following the ICU admission during which a subject receives ECMO, subsequent ICU admissions ("bounce backs") will not be included.

The Data Coordinating Center (DCC) of the CPCCRN estimates that 150 children receive ECMO annually within the network, which admits over 17,000 children per year to the PICU in its eight centers. This estimate is based on the network registry. The initial accrual period will be 4 years, with targeted enrollment of 600 subjects.

2 Rationale and Background

The use of extracorporeal systems such as ECMO is becoming more frequent, as indications for these techniques expand.[1–3] Changes in technology over the past few years have made ECMO circuitry easier to set up and deploy, potentially making it safer and applicable to a wider range of patients.[4, 5] Despite the success of ECMO in supporting

patients to organ recovery, allowing removal of the device and survival from the acute illness, the procedure is not without risks. Bleeding and thrombotic complications are common and adversely affect patient outcome.[6–8] In this project, we seek to assess and quantify the incidence and risks of bleeding and thrombotic complications. In addition, we seek evidence of association of these risks with technological systems used, practice protocol adherence, strategies of coagulation monitoring, and the indications for ECMO use.

Therapeutic maneuvers to avoid bleeding and thrombotic risk requires specific monitoring. Heparin is used most often to maintain circuit integrity.[9] This is a delicate balance: too little anticoagulation increases thrombosis risk while too much anticoagulation may contribute to catastrophic bleeding. Intracranial hemorrhage during ECMO results in morbidity and mortality[10, 11] and may lead to withdrawal of support due to neurologic damage. Thrombosis occurring within the ECMO circuit can lead to device failure and death, and thrombotic events in the children undergoing ECMO can cause limb loss and/or organ system dysfunction from lack of vascular flow to tissues. The most devastating thrombotic complication of ECMO is central nervous system ischemia resulting in stroke.[12–14] Stroke can result in complete neurologic devastation and brain death, early withdrawal of support or long term disability.

The majority of published reports on complications during ECMO come from reviews of the Extracorporeal Life Support Organization (ELSO) registry.[2, 15–19] While the registry has information on over 50,000 patients, it has been criticized for lack of specificity in the data collected, concerns over validation of data from the over 100 centers who submit information and no long term functional assessment in survivors. Nonetheless, the registry is an important source of data which has consistently found that complications occurring during ECMO adversely affect outcome. Complications that are reported to the ELSO registry are listed in the Appendix on page 35; bleeding and clotting contribute to a large portion of these complications.

Bleeding events occur in up to half of pediatric patients undergoing ECMO. Bleeding occurs at surgical sites, cannulation sites, gastrointestinal or pulmonary sites in over a third of patients. Neurologic complications such as cerebral infarction, intracranial bleeding or seizures occur in approximately 15% of children receiving ECMO.[20]

In a recent evaluation of the ELSO registry of 1773 patients who received ECMO between 2005-2011 at eight large children's hospitals that comprise the Collaborative Pediatric Critical Care Research Network (CPCCRN), complications were reported in

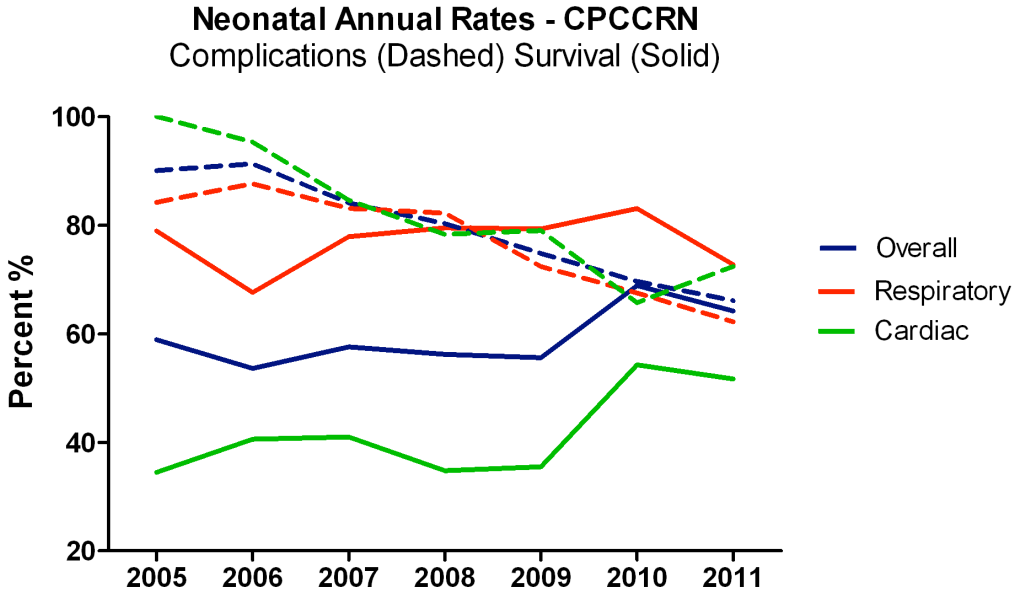

Figure 1: Neonatal survival and complications

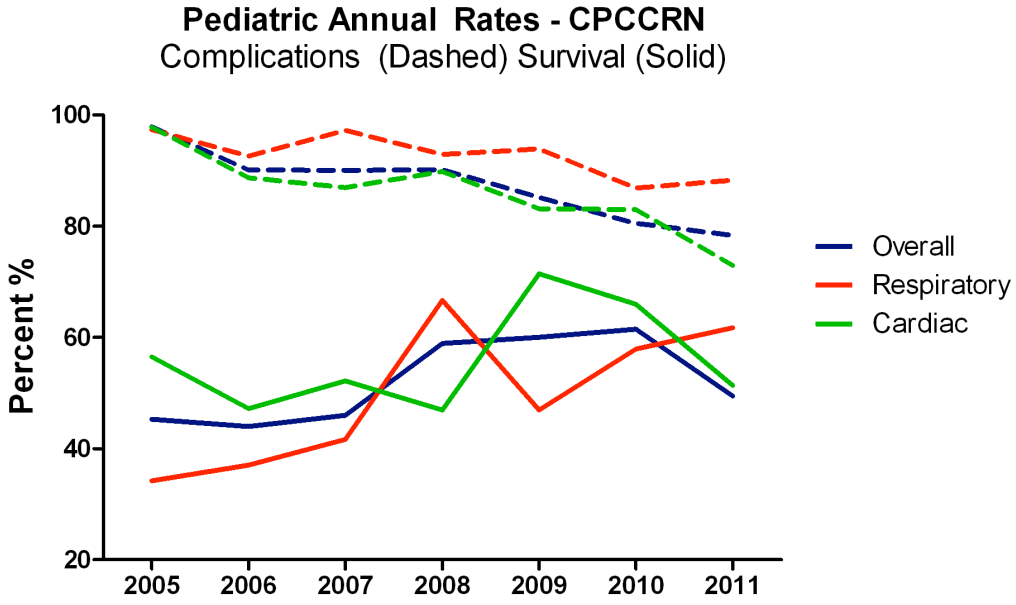

Figure 2: Pediatric survival and complications

85% of patients during the study period, with bleeding and thrombosis occurring in 38% and 31% of patients respectively. (Garcia-Filion, P and Dalton HJ, SPR annual meeting, Boston MA, 2012) Figure 1 on the facing page depicts the time trend of complications and survival in neonates (<30 days of age) and Figure 2 on the preceding page shows similar data for pediatric patients (31 days to 18 years of age) receiving ECMO at CPCCRN sites. In neonates, complications declined (90% to 66%; p<0.001) as overall survival increased (59% to 64%; p=0.10). A similar trend was noted in pediatric patients: complications declined (98% to 78%; p<0.001) as survival increased (45% to 50%; p=0.015).

Table 1: Bleeding and thrombotic complications in respiratory ECMO (excludes congenital diaphragmatic hernia).

	Bleeding			Thrombosis		
Neonatal						
Complications	% (#)	Survival OR	95% CI	% (#)	Survival OR	95% CI
0	74.6 (385)	1	-	73.5 (379)	1	-
1	22.3 (115)	0.26	0.16, 0.40	15.9 (82)	0.35	0.21, 0.58
2	3.1 (16)	0.09	0.03, 0.26	6.2 (32)	0.42	0.20, 0.92
		p<0.001		4.5 (23)	0.29	0.12, 0.69
					p<0.001	
Pediatric						
Complications	% (#)	Survival OR	95% CI	% (#)	Survival OR	95% CI
0	50.4 (133)	1	-	62.9 (166)	1	-
1	32.9 (87)	0.52	0.30, 0.90	21.9 (58)	0.91	0.50, 1.65
2	16.7 (44)	0.24	0.11, 0.51	9.9 (26)	0.91	0.40, 2.08
		p<0.001		5.3 (14)	0.25	0.07, 0.92
					p<0.001	

Bleeding or thrombotic events were the most common complication in both neonatal and pediatric patients in these CPCCRN hospitals. The inverse association of the number of bleeding and thrombotic events and patient outcomes is shown in Table 1 (respiratory ECMO) and Table 2 on the next page (cardiac ECMO). Bleeding was most commonly seen at surgical (17%) and cannulation sites (14%), and intracranial hemorrhage occurred in 11%. Bleeding complications reduced survival by 68% (OR 0.32, CI 0.27, 0.40). Thrombotic events included clots in the membrane oxygenator (12%), hemolysis (10%) and intracranial infarctions (4%). Thrombotic complications reduced survival likelihood by 58% (OR 0.42, CI 0.35, 0.52).

Table 2: Bleeding and thrombotic complications in cardiac ECMO.

	Bleeding			Thrombosis		
Neonatal						
Complications	% (#)	Survival OR	95% CI	% (#)	Survival OR	95% CI
0	56.9 (211)	1	-	67.7 (251)	1	-
1	27.8 (103)	0.56	0.35, 0.92	19.9 (74)	0.29	0.16, 0.53
2	15.4 (57)	0.25	0.12, 0.51	7.8 (29)	0.47	0.21, 1.07
		p<0.001		4.6 (17)	0.14	0.03, 0.62
					p<0.001	
Pediatric						
Complications	% (#)	Survival OR	95% CI	% (#)	Survival OR	95% CI
0	56.3 (200)	1	-	67.3 (239)	1	-
1	30.7 (109)	0.34	0.21, 0.54	19.7 (70)	0.35	0.20, 0.60
2	12.9 (46)	0.35	0.18, 0.68	9.9 (35)	0.23	0.11, 0.49
		p<0.001		3.1 (11)	0.19	0.05, 0.72
					p<0.001	

These results from CPCCRN centers are consistent with reports from other authors. Hervey-Jumper has noted an increased risk of intracranial hemorrhage (ICH) in children as compared to adults and a significant decline in survival in patients with ICH as compared to the overall ECMO population (36% vs 65%).[13] Neonates <34 week gestation are at higher risk of ICH as compared to older patients.[21, 22] These historical reports of increased intracranial hemorrhage in premature infants have precluded them from consideration for ECMO. Advances in cardiac surgery now allow operative repair of congenital heart defects even in small, premature infants thus exposing them to the risk of bleeding from the high levels of anticoagulation which are required and many patients are surviving without devastating intracranial hemorrhage. Postoperative complications may result in need for ECMO support in these fragile premature infants. New technology, especially in the development of low resistance oxygenator devices, is resulting in reconsideration of broader provision of ECMO for premature infants. The impact of these recent technological advances on the incidence of ICH in infants (premature or otherwise) and children has not been measured to date.

Management of anticoagulation is complicated by underlying disease and organ dysfunction present in patients prior to ECMO, equipment setup, and advances in modalities of monitoring. Heparin has been the most commonly used anticoagulant used during

ECMO, traditionally monitored by measuring the activated clotting time (ACT) at the bedside. The correlation between ACT, heparin dose, and the occurrence of clotting and bleeding is poor.[8, 12, 23, 24] Improved understanding of other factors involved in the clotting cascade, as well as improved ability to measure these factors, is resulting in reexamination of anticoagulant practices during ECMO.

Although most centers have algorithms and protocols related to anticoagulation monitoring and treatment for observed abnormalities, there are little data about whether these guidelines are carefully followed, or whether deviation from these protocols impacts adverse event rates. The policies for anticoagulation monitoring and blood transfusion have been obtained from all CPCCRN sites, and the variation of these policies is evident. The varied approaches to anticoagulation monitoring and management makes interpretation of results between centers difficult to extrapolate to the community at large, but provides CPCCRN with an opportunity to seek and describe potential associations between different approaches and observed blood-related adverse events.

3 Significance of the Study

Bleeding and thrombotic events during ECMO support are common and have adverse outcomes on survival and result in increased morbidity, disability and health care expenditures. The science related to anticoagulation management required during ECMO is imprecise and poorly studied. The impact of center-specific ECMO management protocols, adherence to such protocols and observed results has not been evaluated in a systematic manner. Seeking evidence of associations between patient factors, ECMO factors, patient management schemes and protocol adherence in a well-defined manner among CPCCRN sites will provide vital data from which to develop future studies designed to decrease bleeding and thrombotic complications during ECMO support.

3.1 Public Health Impact

The long-term disability associated with bleeding and thrombotic events (particularly strokes) during non-neonatal ECMO has not been well studied. Glass and colleagues identified major disability at age 5 in 17% of children who had survived neonatal ECMO, and in these children with major disability, 53% had suffered ICH or stroke during their ECMO support.[25] Improved understanding of these catastrophic complications during ECMO is needed, particularly in light of new equipment advances and the increasing

exposure of infants to ECMO post-operatively after congenital heart surgery.

3.2 Technology Impact

There have been considerable changes in ECMO equipment during the past several years. There has been a shift from traditional roller head/silicone membrane oxygenator systems to centrifugal pumps and hollow fiber oxygenators. These newer systems are easier to prepare and set up for use, have excellent gas exchange characteristics, and can be used for weeks without need for replacement. However, the superiority of these newer systems is not established.[26–28] Supportive studies have reported decreased blood product requirements, better patient outcomes, and less need for component replacement. Other reports suggest no advantages with respect to hemolysis, platelet aggregation, or need for blood products. Finally, a recent review of the ELSO study noted increased hemolysis, hyperbilirubinemia (OR of 5.49 [2.62-11.59]), and acute renal failure (OR of 1.61 [1.10-2.39]) with centrifugal pumps (Barrett CS, et al.; unpublished results). These conflicting data support the importance of this protocol to thoroughly describe ECMO practices in CPCCRN centers, and carefully quantify and understand the adverse events most associated with long term patient outcomes (bleeding and thrombotic complications). Since the CPCCRN centers vary with respect to specific equipment choices, the network is positioned to seek and describe potential associations between equipment and adverse event rates.

3.3 Summary

Bleeding and thrombotic events during ECMO support are common and have adverse outcomes on survival and result in increased morbidity, disability and health care expenditures. The science related to anticoagulation management required during ECMO is imprecise and poorly studied. The impact of center-specific ECMO management protocols, adherence to such protocols, and observed outcomes has not been evaluated in a systematic manner with recent ECMO equipment. This prospective observational cohort study of neonates, infants, and children requiring ECMO in CPCCRN centers will provide important descriptive and exploratory data from which to develop future studies designed to decrease bleeding and thrombotic complications during ECMO support.

4 Study Design and Data Collection

4.1 Study Design

A granular evaluation of hemostatic monitoring practices and treatment has not been conducted in a systematic, multicenter fashion. Research into practice variation in order to establish standardized, evidence-based monitoring and treatment protocols may reduce complication rates. This prospective observational cohort study of ECMO patients seeks evidence of the association of monitoring practices with bleeding and thrombotic complications.

4.2 Data Collection

Subjects enrolled in this protocol may have multiple ICU admissions. For purposes of this study, the ICU admission during which ECMO was carried out is the only ICU admission that will be included in data collection.

Study day 1 is the day of ECMO initiation (i.e., start of flow). Each study day, including day 1, will be based on a calendar day starting at midnight (00:00 hours) and ending at 23:59 hours.

For patients who may receive more than one episode of ECMO support, only data from the first ECMO run will be included. If patients are transitioned from ECMO to a longer term support device, such as a ventricular assist device (VAD), daily data collection will cease at the end of the study day. For patients who are successfully decannulated from ECMO, daily data collection will cease at the end of the following study day after ECMO is discontinued. Discharge information will be collected upon patient's discharge from ICU and hospital. In the case of death, daily data collection will stop at the time of death and death-related information will be collected.

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

4.2.1 Patient Information

Patient demographic information:

1. Date of birth of subject

2. Gestational age at birth (if newborn, <30 days)
3. Gender of subject
4. Race of subject
5. Ethnicity of subject
   (a) Hispanic or Latino
   (b) Not Hispanic or Latino

Patient ICU diagnoses

1. Primary diagnosis
2. Secondary diagnoses
3. Chronic diagnoses

Patient history of technology dependence:
Before the hospital admission requiring ECMO (e.g., at home, in a chronic care facility, etc.), did the subject require any of the following medical devices (obtain by review of chart):

1. Gastrostomy tube (yes/no)
2. Other feeding tube (yes/no)
3. Oxygen (yes/no)
4. Tracheostomy (yes/no)
5. Home ventilator (yes/no)
6. Ventricular shunt (CSF) (yes/no)
7. Chronic dialysis (yes/no)
8. Chronic vascular access (yes/no)

Patient baseline measurements:
Date of measurement will be collected for the following:

1. Weight (kg)
2. Length (cm)
3. Head circumference (cm)

Patient baseline cardiovascular status:

1. Vasoactive - inotrope score (date and time)
2. Were any bolus vasoactive medications given in the hour prior to ECMO initiation? (yes/no)

Patient baseline ventilator status:
Baseline ventilator settings along with the associated date and time will be collected.

1. Mode (volume control, pressure regulated volume control, pressure control, high frequency oscillatory ventilation, other)
2. Ventilator Rate
3. PIP
4. Tidal volume exhaled
5. Set tidal volume
6. PEEP
7. Pressure support
8. FiO_2
9. Mean airway pressure
10. Frequency (HFOV)
11. Amplitude (HFOV)

Patient baseline laboratory values:
Date and time will be collected for the following laboratory values:

1. Arterial blood gas
2. Comprehensive metabolic panel
3. Lactate
4. Coagulation studies
5. Hematology

Patient baseline vital measurements:
Date and time will be collected for the following measurements:

1. Heart rate
2. Respiratory rate
3. Systolic and diastolic blood pressure, mean blood pressure
4. Temperature
5. Pupillary reflex

Patient Baseline Infection Information:
The culture collection date and time will be collected for the following:

1. Was a culture- or PCR-proven bacterial or fungal infection diagnosed prior to ECMO initiation? (yes/no); if yes, upload report
2. Was a culture- or PCR-proven viral infection diagnosed prior to ECMO initiation? (yes/no); if yes, upload report

3. Was an unproven, suspected infection diagnosed and treated with antibiotics, antifungals, or antivirals prior to ECMO initiation? (yes/no); if yes specify:
   (a) bacterial
   (b) fungal
   (c) viral

Patient functional status:

1. POPC/PCPC
2. FSS

4.2.2 Hospitalization Information

1. Date and time of hospital admission
2. Date and time of admission to ICU
3. Date and time of discharge from ICU
4. Date and time of discharge from hospital
5. Vital status at hospital discharge
6. If died, did this follow withdrawal of support? (yes/no)
7. Date and time of death

4.2.3 ECMO Information

Initiation of ECMO:

1. Site of ECMO care (PICU, NICU, CICU)
2. Primary ECMO indication
   (a) Respiratory
   (b) Cardiac
   (c) ECPR
3. Does the child have meconium aspiration syndrome? (yes/no)
4. Does the child have congenital diaphragmatic hernia? (yes/no)
5. Does the child have persistent pulmonary hypertension? (yes/no)
6. Does the child have congenital cystic adenomatoid malformation? (yes/no)
7. Operative procedures in 24 hours prior to ECMO initiation (yes/no); if yes, date and time

8. Cardiopulmonary bypass in 24 hours prior to ECMO initiation (yes/no); if yes, date and time
9. ECMO initiation date and time
   (a) Was patient placed on ECMO directly from cardiopulmonary bypass (yes/no)
   (b) Was patient placed on ECMO by way of an EXIT procedure? (yes/no)
10. Heparin bolus for cannulation (yes/no); if yes specify:
   (a) Dose (units/kg)
11. Time to initial heparin infusion after ECMO initiation (hours, <1, ≥1 to 2, >2 to 3, > 3)
12. First patient ACT on ECMO (if measured)(date and time)

ECMO Equipment and Setup:

Since the specific equipment used for ECMO may affect coagulation and hemolysis, specific data will be obtained about the technology used for ECMO in each subject. These data elements include the following list:

1. Mode of ECMO
2. Pump manufacture/model
   (a) Centrifugal (yes/no); if yes specify pump ID
   (b) Roller head (yes/no); if yes specify pump ID
3. Bladder/venous reservoir (yes/no)
4. Oxygenator
   (a) Silicone lung (yes/no)
   (b) Hollow fiber (yes/no); if yes specify:
      i. Medtronic
      ii. Quadrox
      iii. Lilliput
      iv. Medos
      v. Terumo
      vi. Other (specify)
   (c) Size
5. Circuit tubing characteristics
   (a) Vendor (specify)
   (b) Coating (yes/no); if yes specify:
      i. Carmeda coated
      ii. Bioline
      iii. Safeline

iv. Other (specify)

6. Circuit bridge
   (a) In-line with stopcocks
   (b) In-line but clamped
   (c) Not in-line
7. Negative pressure monitoring (yes/no)
8. Priming of circuit
   (a) Non-blood primed circuit
      i. Hemodilution correction strategy
         A. None
         B. Exchange transfusion
         C. Hemofiltration
         D. Other (specify)
   (b) Blood primed circuit
9. Priming volume (cc)
10. Cannula characteristics (each inserted cannula will be documented for this study along with initiation and discontinuation date and time)
   (a) Venous cannula
      i. Vendor (specify)
      ii. Size
      iii. Site: (specify)
   (b) Arterial cannula
      i. Vendor (specify)
      ii. Size
      iii. Site: (specify)
   (c) Double lumen catheter (yes/no); if yes specify:
      i. Vendor (specify)
      ii. Size
      iii. Site: (specify)
   (d) Cephalad cannula (yes/no)
   (e) Left atrial (LA) drainage cannula (yes/no)
   (f) Distal perfusion cannula (yes/no); if yes specify:
      i. Site (specify)

4.2.4 Daily Information

Daily transfusion history data:

1. Whole blood (yes/no); if yes specify:
   (a) Amount given (total mL) (prime)
   (b) Amount given (total mL) (non-prime)
2. Packed red blood cells (yes/no); if yes specify:
   (a) Amount given (total mL) (prime)
   (b) Amount given (total mL) (non-prime)
3. Platelets (yes/no); if yes specify:
   (a) Amount given (total mL)
4. Plasma (yes/no); if yes specify:
   (a) Amount given (total mL)
5. Cryoprecipitate (yes/no); if yes specify:
   (a) Amount given (total mL)
6. ATIII (yes/no); if yes specify:
   (a) Total dose given on this study day
7. Novoseven (yes/no); if yes specify:
   (a) Total dose given on this study day
8. Amicar (yes/no); if yes specify:
   (a) Loading dose prior to infusion (yes/no)
   (b) Infusion (yes/no)
   (c) Total dose given on this study day

Daily laboratory information

1. Parameter daily goals:
   (a) Hemoglobin or hematocrit goal
   (b) Platelet goal
   (c) PT/PTT goal
   (d) Fibrinogen goal
   (e) Anti Xa goal
   (f) ATIII goal
   (g) ACT goal
   (h) PaO_2 goal
   (i) $PaCO_2$ goal
   (j) pH goal
   (k) Temperature goal
   (l) SvO_2 goal
   (m) SaO_2 goal

2. Laboratory values (values closest to 7:00 am will be documented along with the date and time):
   (a) Arterial blood gas
   (b) Comprehensive metabolic panel
   (c) Lactate
   (d) Coagulation studies
   (e) Hematology
   (f) Plasma free hemoglobin

Daily ventilator settings

Ventilator settings along with the associated date and time will be collected once per study day, closest to 7:00 am.

1. Mode (volume control, pressure regulated volume control, pressure control, high frequency oscillatory ventilation, other)
2. Ventilator Rate
3. PIP
4. Tidal volume exhaled
5. Set tidal volume
6. PEEP
7. Pressure support
8. FiO_2
9. Mean airway pressure
10. Frequency (HFOV)
11. Amplitude (HFOV)

Daily vital measurements

1. Heart rate
2. Respiratory rate
3. Systolic and diastolic blood pressure, mean blood pressure
4. Temperature
5. Pupillary reflex

Daily ECMO related data:

1. Was the subject separated from ECMO on this study day? (yes/no); if yes specify:
   (a) Date and time of decannulation
   (b) Status at time of decannulation (alive/dead/transition to VAD)

   (c) On the day of decannulation, what was the flow rate one hour before decannulation?
2. Was a new culture- or PCR-proven infection diagnosed on this study day? (yes/no); if yes, upload report
3. Blood loss history
   (a) Total blood loss for laboratory sampling (cc)
   (b) Total chest tube output (cc) (If no chest tube, record zero)
   (c) Surgical site bleeding requiring transfusion (yes/no)
   (d) Cannula site bleeding requiring transfusion (yes/no)
   (e) Gastrointestinal bleeding requiring transfusion (yes/no)
   (f) Pulmonary hemorrhage requiring transfusion (yes/no)
   (g) Sanguineous chest tube output requiring transfusion (yes/no)
   (h) Laboratory sampling blood loss requiring transfusion (yes/no)
   (i) New or increased intracranial bleeding (yes/no)
4. Thrombotic events
   (a) Did any of the following thrombotic events occur on this study day (record all that apply)
      i. Intracranial infarction
      ii. Limb ischemia
      iii. Pulmonary embolus
      iv. Intracardiac clot
      v. Aortopulmonary shunt clot
      vi. Hemolysis (plasma hemoglobin >50 mg/dL)
      vii. Other (specify)
   (b) If yes specify
      i. New
      ii. Better
      iii. Same
      iv. Worse
5. Did the patient have any clots requiring circuit component change-out on this study day? (yes/no)
   (a) If yes, which circuit components had clots?
      i. Oxygenator
      ii. Bridge
      iii. Bladder
      iv. Hemofilter
      v. Pump head
      vi. Tubing

vii. CVVH circuit
viii. Arterial cannula
ix. Venous cannula
x. Other circuit component

(b) Was the entire circuit replaced? (yes/no)
i. If no, which circuit components were changed out?
A. Oxygenator
B. Bridge
C. Bladder
D. Hemofilter
E. Pump head
F. Tubing
G. CVVH circuit
H. Arterial cannula
I. Venous cannula
J. Other circuit component

6. Were circuit components changed out due to non-thrombotic events on this study day? (yes/no)
(a) If yes, was the entire circuit replaced? (yes/no)
i. If no, which circuit components were changed out?
A. Oxygenator
B. Bridge
C. Bladder
D. Hemofilter
E. Pump head
F. Tubing
G. CVVH circuit
H. Arterial cannula
I. Venous cannula
J. Other circuit component
7. Were there any complications during circuit component change-out? (yes/no); if yes specify:
(a) Cardiac arrest
(b) Hypoxemia requiring hand ventilation or increasing ventilator settings
(c) Increase in vasoactive agents or bolus vasoactive administration
8. Flow rate, closest to 7:00 am (mL/min)
9. SvO_2, closest to 7:00 am
10. Did the child have CVVH on this study day? (yes/no)

11. Did the child have plasmaphoresis on this study day? (yes/no)
12. Did the child have hemofiltration on this study day? (yes/no)
13. Was the ECMO tubing (not bridge) clamped for more than one hour on this study day? (yes/no)

Hospital discharge data:

1. POPC/PCPC at discharge from hospital
2. Functional Status Score (FSS) at discharge from hospital
3. Did patient require (information at hospital discharge only):
   (a) Gastrostomy tube (yes/no)
   (b) Other feeding tube (yes/no)
   (c) Oxygen (yes/no)
   (d) Tracheostomy (yes/no)
   (e) Home ventilator (yes/no)
   (f) Ventricular shunt (CSF) (yes/no)
   (g) Chronic dialysis (yes/no)
   (h) Chronic vascular access (yes/no)

5 Data Analysis

Specific Aim 1. Measure the incidence of bleeding and thrombotic complications in a prospective cohort of children receiving ECMO.

The primary analysis for this Aim will assess proportion of patients who have bleeding complications and who have thrombotic complications. Proportions will be reported along with 95% confidence intervals. This analysis will be performed overall, as well as within subgroups of patients treated for cardiac and respiratory support.

Secondary analyses for this Aim will examine rates of each type of event, incorporating multiple events per patient when these occur. Numbers of events per hours of ECMO will be reported, together with 95% confidence intervals. Confidence intervals will be generated using parametric approaches if appropriate (for example, if numbers of events approximately follow a Poisson distribution), and by alternative approaches such as bootstrap otherwise.

Specific Aim 2. Quantitatively and qualitatively describe monitoring practices for anti-coagulation.

This Aim will involve descriptive reporting of practices across the CPCCRN centers.

Specific Aim 3. Seek evidence of association between bleeding and thrombotic complications, laboratory coagulation measurements, patient characteristics, ECMO circuitry, and adherence to center-specific ECMO management protocols.

This Aim is considered exploratory and will involve assessment of associations, univariate and adjusted, of various factors with complications considered as binary outcomes and rates. Patient factors and ECMO circuitry data to be assessed for association with outcomes are listed in the Data Collection section above. For quantifying adherence to protocol, a key measure used will be the proportion of ECMO algorithm factors that were adhered to. The proportion of factors adhered to may be collapsed into groupings, e.g. <25%, 25-50%, 50-75%, or 75% or greater. Adherence will be calculated on a daily basis, when complete data are available, and summarized as an average over all ECMO days for a particular patient.

Primary analyses will analyze associations of factors with binary outcomes on a per-patient basis. For determining univariable associations at a patient level (not taking time of event(s) into account), appropriate measures of significance will include chi-squared tests for categorical factors. Continuous factors will be analyzed as continuous data using approaches including logistic regression, although these may be categorized, using clinically relevant cutpoints when possible and data quartiles otherwise, for initial assessments of association. Logistic regression will be used to assess multivariable associations when appropriate.

While the above analyses have the advantage of simplicity, they do no account for multiple events per patient and the time to event. Therefore, factors will also be examined for association with event rates per ECMO day, and for association with time until an event occurs. General approaches for these analyses will include Poisson regression and its extensions for rate analyses, and Kaplan-Meier plots/Cox regression analyses for time to event outcomes.

Secondary analyses will analyze data on a per-day basis, making maximal use of daily data collection of laboratory values and adherence measurements. We note that these analyses will be limited by the cross-sectional nature of the data collected (a morning data value may not, for example, reflect the patient's worst value for that measurement over the entire day). We expect Generalized Estimating Equations (GEE) to be of utility for analyzing such correlated daily outcome data.

Power Considerations

While the sample size in this study was in part determined by numbers of available patients, precision calculations were performed to assure sufficient sample size for the first primary Aim. Specifically, a retrospective analysis identified bleeding and/or thrombotic complications in approximately 30% of patients that underwent ECMO. Assuming that we find a similar proportion in the prospective study, sample sizes of 300 subjects (expected for the cardiac and respiratory subgroups) and 600 subjects (entire sample) will provide two-sided 95% CIs that extend 5.3% and 3.7% in each direction from the observed value, respectively.

6 Data Management

6.1 Electronic Data Capture System

In this study, de-identified medical records will be provided to the expert reviewers via a secure electronic website which is maintained at the DCC. Quality assessments and data elements will be entered into the electronic data capture (EDC) system used at the DCC, which can be accessed via any Internet web browser. All research coordinators, investigators, and reviewers will be trained through an in-person training session before the start of the project, and topics will include data abstraction, collection, and the data entry process.

6.2 Data Security

The DCC is located at the University of Utah in Salt Lake City, Utah. The DCC has a state-of-the-art computer infrastructure with a dedicated server room with a fire suppression system, air conditioning, and separate air filtering. The server facility is locked separately from the remainder of the DCC and access to the building is monitored by security personnel year round. The DCC coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the DCC with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. The electronic data capture system (EDC), eRoom^{TM} (Web-based

collaborative workspace), and other web applications use the SSL protocol to transmit data securely over the Internet. Direct access to DCC machines is only available while physically located inside the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against DCC servers, and DCC IT staff are notified of intrusion alerts.

Servers are backed up daily through a dedicated backup server and internal high speed network. Incremental backups occur hourly and nightly. Full system backups occur nightly and weekly with off-site rotations. Security is maintained with Windows 2008 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 6 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

6.3 Data Confidentiality

The investigators and staff of the DCC are fully committed to the security and confidentiality of all data collected for CPCCRN studies. All DCC personnel at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

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

6.4 Data Quality Management and Monitoring

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

Remote monitoring: The DCC will supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and telephone consultations with the Clinical Center investigator and/or research coordinator to review data quality. This requires uploading de-identified copies of

specific parts of the medical record to the DCC staff, who review those materials against the data recorded in the electronic data capture system.

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

6.5 Record Access

The medical record must be made available to authorized representatives of the DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the National Institutes of Health, and the Institutional Review Board (IRB) for each study site, if appropriate.

7 Protection of Human Subjects

Institutional Review Board (IRB) Approval The DCC and each clinical center must obtain approval from their respective IRB prior to participating in the study. The DCC will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

Potential Risks and Benefits: There are no physical risks associated with participating in this study, as this is an observational study and no therapeutic intervention is being tested. There is a minor risk of loss of confidentiality. This is mitigated by data security procedures at the DCC (Section 6.2 on page 27). The benefit from this study is that better understanding of the incidence of bleeding and clotting complications may lead to strategies to reduce these complications during ECMO in future critically ill children.

Protection Against Risks: Data security (Section 6.2 on page 27) and confidentiality (Section 6.3 on page 28) procedures at the DCC have been described. Patient information is sent to the DCC to enable proper data validation and accurate coding of such data 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 the Health Insurance Portability and Accountability Act (HIPAA). This analytical database will be the only one available for the analysis of the current and future derivative studies.

Informed Consent: Waiver of consent is requested for observational data collection for each ECMO patient eligible for this study. The justification for waiver of consent for observational data collection concerning ECMO and blood product administration is based on the following factors:

1. The scientific validity of the study is dependent on capturing all ECMO patients during the period of study, as one of the major goals is to accurately describe the incidence of complications in the ECMO population.

2. The study involves no intervention.

3. The minimal risk of loss of privacy is mitigated by secure data management at the DCC, and analysis datasets will be de-identified.

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

8 Health Insurance Portability and Accountability Act

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

9 Inclusion of Women and Minorities

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

10 Retention of Records

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

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Appendix

Complications are recorded in the ELSO registry in two major categories: mechanical and patient-related. Within the patient-related complications, there are eight subcategories, as shown in the listing:

Mechanical
- Oxygenator failure
- Raceway rupture
- Other tubing rupture
- Pump malfunction
- Heat exchange malfunction
- Air in circuit
- Cracks: connectors
- Cannula problems

Patient-related
- *Thrombotic*
  - Intracranial infarction
  - Clots: oxygenator
  - Clots: bridge
  - Clots: bladder
  - Clots: hemofilter
  - Clots: other
- *Hemorrhagic*
  - Intracranial hemorrhage
  - Gastrointestinal hemorrhage
  - Cannulation site bleeding
  - Surgical site bleeding
  - Hemolysis (hgb>50mg/dL)
  - Disseminated intravasc coag (DIC)
  - Pulmonary hemorrhage
- *Cardiopulmonary complications*
  - Inotropes on ECMO
  - Myocardial stun (by echo)
  - CPR required
  - Cardiac arrhythmia
  - Hypertension requiring dilator
  - PDA: right to left
  - PDA: left to right
  - PDA: bidirectional
  - PDA: unknown
  - Tamponade: blood, serous, air
- *Pulmonary pneumothorax*
- *Neurologic complications*
  - Clinical brain death
  - Clinical seizures
  - EEG-detected seizures
- *Infectious complications*
- *Renal complications*
  - CAVHD required
  - Creatinine 1.5 to 3.0
  - Creatinine >3.0
  - Dialysis required
  - Hemofiltration required
- *Metabolic complications*
  - Glucose <40
  - Glucose >240
  - Hyperbilirubinemia
  - pH <7.2
  - pH >7.6