Pediatric ECMO and Cefepime (PEACE)
CPCCRN Protocol Number 059

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

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

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PROTOCOL TITLE:

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Lead Investigator and Author:
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Children's Hospital of Philadelphia

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

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Extracorporeal membrane oxygenation (ECMO) is used in the care of critically ill children. ECMO has been known to impact pharmacokinetics (PK). Antibiotics are administered to treat infections in critically ill children. Sub-therapeutic concentrations can lead to treatment failures and supra-therapeutic concentrations can lead to toxicity. Knowledge regarding the impact of ECMO on cefepime PK is essential for accurate dosing in this population.

This study will seek to gain preliminary knowledge on the impact of ECMO on the PK of cefepime administered as standard of care and to examine the variability in cefepime PK in infants receiving ECMO.

1 Study Summary

1.1 Hypotheses

The hypotheses of this prospective pharmacokinetic study are:

1. The volume of distribution of cefepime is increased, and the clearance is reduced in patients receiving ECMO.
2. There will be variability in cefepime pharmacokinetics across different circuit types.

1.2 Specific Aims

This study has the following Specific Aims:

Specific Aim 1. To gain preliminary data on the impact of ECMO on the pharmacokinetics of cefepime administered as standard of care to infants.

Specific Aim 2. To examine the variability in cefepime pharmacokinetics in infants receiving ECMO.

1.3 Subject Eligibility, Accrual and Study Duration

Inclusion Criteria:

A patient will be eligible for enrollment if s/he:

- is currently receiving ECMO therapy; AND

- is $\geq$ 30 days and $<$ 2 years of age; AND
- is receiving IV cefepime as standard of care; AND
- is receiving renal replacement therapy (e.g., CVVH, ultrafiltration).

Exclusion Criteria:

A patient will be ineligible for enrollment if s/he:

- is requiring ongoing massive blood product transfusion for hemorrhage; OR
- is receiving therapeutic plasma exchange; OR
- has been enrolled in this study previously.

At least 40 subjects will be enrolled. Enrollment will continue until the cohort is considered evaluable, see Section 6.1 on page 16. It is anticipated that accrual will take approximately 36 months.

2 Rationale and Background

Extracorporeal membrane oxygenation provides partial or complete support for patients with severe cardiopulmonary failure, and can be used as a bridge to recovery to mechanical support/organ replacement. Veno-venous (VV) ECMO supports the lungs whereas veno-arterial (VA) ECMO provides support for both the heart and lungs. The impact of ECMO on the PK of commonly used intensive care drugs should be fully understood to ensure optimal drug therapy, minimal toxicity and improve patient outcomes. Unknown interactions between ECMO and pharmacotherapy may seriously impair patient recovery.

In critically ill patients not receiving ECMO, numerous PK studies have demonstrated highly significant changes to drug exposure through interactions between the patient, pathology and the drug. The ECMO system introduces additional variables, which are inherent to the circuit itself, as well as the systemic inflammation that results from use of an extracorporeal circuit. Sequestration of drugs in the circuit, increased volume of distribution (Vd) and decreased clearance (CL) are the major PK changes associated with ECMO,[1] although the extent of such changes remains poorly characterized. Neonatal studies have reported significant alterations in antibiotic, sedative and analgesic disposition.[2] Recently, significant antibiotic, sedative and analgesic drug sequestration has

been demonstrated in ECMO circuits used for adult patients.[3] The type and age of circuit components including the type of the pump, oxygenator and tubing, as well as circuit priming, may influence the level of drug sequestration.[4–7] Patient factors such as systemic inflammation, hemodilution, bleeding and transfusion, organ dysfunction and renal replacement therapy (RRT) all add to the clinical challenges of drug dosing during ECMO.[8, 9] In addition, individual centers use different techniques when building their respective ECMO circuit. The amount of variability in drug disposition and pharmacokinetics that is introduced by different circuit components is largely unknown.

Preliminary data shows that standard dosing of 50 mg intravenously q12 hours achieves concentrations above 8 mg/ml, representative of the MIC90 for pseudomonas. The impact of renal replacement therapy during ECMO on plasma concentrations is unclear. We hypothesize that renal replacement therapy and ultrafiltration will result in increased removal of cefepime, and subsequently lower concentrations.

2.1 Cefepime

Certain antimicrobials such as vancomycin can be dose adjusted based on available therapeutic drug monitoring. However, there are many life-saving antimicrobials that are used in the ECMO setting that do not have available therapeutic drug monitoring, such as cefepime.

Cefepime is a fourth generation cephalosporin that is effective against pseudomonas. It is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime is highly resistant to hydrolysis by most β-lactamases, has a low affinity for chromosomally-encoded β-lactamases and exhibits rapid penetration into gram-negative bacterial cells. It is often the first line for suspected gram-negative infection in a child with a fever who has a central line or is receiving ECMO therapy. The dosing for the treatment of bloodstream infections and meningitis is 50 mg/kg/dose every 8 hours for 7-10 days (maximum dose: 2 grams every 8 hours).

Cefepime PK have been evaluated in pediatric patients following single and multiple 50 mg/kg doses on q8h (n = 29) and q12h (n = 13) schedules. The mean ($\pm$ SD) age of the patients was 3.6 ($\pm$ 3.3) years, and ranged from 2.1 months to 11.2 years. Following a single IV dose, total body clearance and the steady state volume of distribution averaged 3.3 ($\pm$ 1.0) mL/min/kg and 0.3 ($\pm$ 0.1) L/kg, respectively. The overall mean elimination half-life was 1.7 ($\pm$ 0.4) hours. The urinary recovery of unchanged cefepime was 60.4

(± 30.4) % of the administered dose, and renal clearance was the primary pathway of elimination, averaging 2.0 (± 1.1) mL/min/kg. There were no significant differences in the pharmacokinetics of cefepime among pediatric patients of various ages or between male (n = 25) and female patients (n = 17). There was no evidence of accumulation of cefepime in patients treated for up to 14 days with either regimen. The exposure to cefepime, including minimum plasma concentrations at steady state, following a 50 mg/kg IV dose in a pediatric patient is comparable to that in adults treated with a 2 g IV dose.[10]

Cefepime has been associated with a greater risk of mortality than other β-lactams in patients treated for severe sepsis. Cefepime's PK and efficacy were examined in a prospective non-interventional study of 21 consecutive intensive care unit (ICU) adult patients treated with cefepime for nosocomial pneumonia.[11] Patients (median age 55.1 years, range 21.8 to 81.2) received intravenous cefepime at 2 grams every 12 hours for creatinine clearance (CLCr) $\geq$ 50 mL/min, and 2 grams every 24 hours or 36 hours for CLCr $<$ 50 mL/minute. Cefepime plasma concentrations were determined at several time-points before and after drug administration by high-pressure liquid chromatography. Pharmacokinetic/pharmacodynamic (PD) parameters were computed by standard non-compartmental analysis. Seventeen first-doses and 11 steady states were measured. Plasma levels varied greatly between individuals, from two- to three-fold at peak-concentrations to up to 40-fold at trough-concentrations. Nineteen out of 21 (90%) patients had PK/PD parameters comparable to literature values. Twenty-one of 21 (100%) patients had appropriate duration of cefepime concentrations above the minimum inhibitory concentration (MIC) for the pathogens recovered in this study (MIC $\leq$ 4 mg/L), but only 45 to 65% of them had appropriate coverage for potential pathogens with cefepime MIC $\geq$ 8 mg/L. Moreover, 2/21 (10%) patients with renal impairment (CLCr $<$ 30 mL/minute) demonstrated accumulation of cefepime in the plasma (trough concentrations of 20 to 30 mg/L) in spite of dosage adjustment. Both had symptoms compatible with non-convulsive epilepsy that were not attributed to cefepime-toxicity until plasma levels were disclosed to the caretakers and symptoms resolved promptly after drug arrest. The authors confirmed the suspected risks of hidden side-effects and inappropriate PK/PD parameters (for pathogens with upper-limit MICs) in a population of ICU adult patients. In addition these data identified a safety and efficacy window for cefepime doses of 2 g every 12 hours in patients with a CLCr $\geq$ 50 mL/minute infected by pathogens with cefepime MICs $\leq$ 4 mg/L. The authors recommended prompt monitoring of cefepime plasma levels in cases of lower CLCr or greater MICs.

2.2 Summary

Given the need for therapeutic concentrations to ensure efficacy and the desire to not exceed these concentrations to avoid toxicity, data regarding the impact of ECMO on cefepime disposition is warranted. This pilot study will provide preliminary data on the variability in cefepime disposition in pediatric patients receiving ECMO therapy, specifically with regards to site dependent differences in circuit components, and will explore the variability in drug clearance across sites. In the event that the variability in PK is large between sites, these preliminary data can be used in simulations to design larger multi-center prospective PK studies. The data generated from the completion of this study can also be used as preliminary data for an NIH sponsored R01 that will focus the development of rational dosing guidelines of sedative, analgesic, anti-infective, anti-epileptic and cardiovascular agents for children receiving ECMO therapy.

3 Study Design

This is a multicenter pharmacokinetic study of cefepime administered as standard of care to infants receiving ECMO therapy who receive renal replacement therapy.

3.1 Screening and Enrollment

Patients receiving ECMO therapy will be screened at least daily for eligibility criteria. Once eligibility criteria are met, the parent(s) or legal guardian(s) will be approached for consent.

3.2 Treatment and Follow-up

During the treatment phase, subjects will receive cefepime as standard of care and undergo PK sampling. There is no follow-up phase for this study.

4 Study Medication and Procedures

4.1 Study Medication Dosing and Accountability

All subjects will receive intravenous cefepime as part of standard of care. The clinical care team will determine the dose and all dose titrations. Drug will be stored, dispensed and logged in the sites' pharmacy, as per pharmacy standard.

4.2 Pharmacokinetic Sampling Schedule

For each subject, PK sampling will occur for two cefepime doses separated in time by at least 36 hours. Antibiotics may be administered either every 6, 8, 12, 18 or 24 hours. PK sampling will vary based on dosing interval and will occur at times indicated in the sampling scheme (see Table 1). Note, PK sampling times are approximate but should be collected as closely as possible to the goal time.

Table 1: PK sample collection schedule by antibiotic dosing.

Interval	Pre-dose	15	30	60	90	120	180	240	300	360	480	600	720	1080	1440	N
			Minutes			(2h)	(3h)	(4h)	(5h)	(6h)	(8h)	(10h)	(12h)	(18h)	(24h)	
Q6h	X	X	X	X	X	X	X	X	X	X						10
Q8h	X	X	X	X	X	X	X	X		X	X					10
Q12	X	X	X		X	X		X		X	X	X	X			10
Q18	X	X	X	X		X		X		X		X	X	X		10
Q24	X		X	X	X	X		X			X		X	X	X	10

If the subject is transitioned from a less frequent to a more frequent dosing regimen (e.g., dosing changed from every 24 hours to every 6 hours) **during the sampling period**, PK sampling will continue as scheduled until the next dose is due; a PK sample will be obtained before the administration of the next dose, and then sampling will stop.

The **total** maximum amount of blood drawn is 20 mL. All study subjects will be receiving ECMO therapy, and thus have a larger circulating blood volume. Therefore, the 20 mL of blood required for this study will not increase the transfusion risk of study subjects.

4.3 Sample Collection and Handling Instructions

The blood volume of each PK sample will be one milliliter. Pharmacokinetic samples preferably will be obtained from an arterial catheter, but can also be obtained from a central catheter or peripheral catheter. PK samples should not be drawn from lumens that have been used to administer cefepime. Every attempt will be made to coordinate PK sampling with the timing of clinical lab draws to minimize the number of times a central line is accessed. Central or arterial lines that are used for PK sampling will be in place for clinical indications, and not placed for the purpose of this study.

4.3.1 Blood Sample Processing

Blood will be obtained, transferred to labeled lithium heparinized tubes, and placed on ice immediately after drawing. Tubes will be centrifuged within 30 minutes (3400RPM X 15 min at 4° Celsius or the sample processing method standardly used for plasma separation at the participating institution). The plasma will be removed and placed in the supplied labeled plasma aliquot tubes. Plasma will be frozen at -70° Celsius or colder until shipped and assayed.

4.3.2 Sample Labeling

Plasma aliquot tubes will be labeled with bar codes that correspond to the specific sample on the PK Sample Worksheet. The subject's study number, and the date and time the sample was drawn will be documented on the worksheet by the person obtaining the sample, or the research coordinator at the bedside. Plasma aliquot tube labels will be provided by Children's Hospital of Philadelphia.

4.4 Subject Completion/Withdrawal

4.4.1 Withdrawal and Removal

Parents may withdraw permission for further sampling at any time. The subject may also be discontinued from the study at the discretion of the Investigator to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

4.4.2 Off-Study Criteria

No further study procedures will be done to a subject (except data analysis) that is deemed off-study. Subjects will be considered off-study if one of the following is met:

- Last target PK sample obtained
- Removed from ECMO
- Removed from renal replacement therapy
- Current prescription of cefepime discontinued
- Death
- Subject removed from study for reasons detailed in 4.4.1

5 Data Collection

Subjects enrolled in this protocol may have multiple ICU admissions. The subject may only be enrolled in this study once. If patients are transitioned from ECMO to a longer term support device, such as a ventricular assist device (VAD), PK sampling will cease. For patients who are successfully decannulated from ECMO, PK sampling will cease.

Data elements for this study include:

- Demographic information:
  - Date of birth
  - Sex
  - Race
  - Ethnicity
  - Length/Height
- Diagnoses:
  - Primary diagnosis
  - Chronic diagnoses
- ECMO-related data:
  - ECMO start date and time
  - Mode of ECMO
  - ECMO pump type (centrifugal or roller head)
  - ELSO registry pump ID
  - Start date of current oxygenator
  - Type of oxygenator (silicone lung or hollow fiber)
  - Size of oxygenator (m^2)
  - Oxygenator coating
  - Circuit tubing coating
  - Circuit priming amounts
- RRT-related data

  - Type of RRT
  - Date and time started
  - All start and stop dates and times
  - Any changes to the type of RRT

- PK sampling- and antibiotic-related data:
  - Weight (dosing-weight used for each dose of cefepime)
  - Date, time, and dose (in mg) of each dose of cefepime
  - Body temperature
  - Date and time of PK samples
  - PK sample collection site
  - Amount of blood collected (mL)
  - Blood product transfusion amounts during PK sampling
- Concomitant medications
- Measures of renal and hepatic function as performed as standard of care one day prior to first dose that is sampled through the end of the day the last dose is sampled (and all in between)
- Daily fluid balance
- If subject withdraws, reason for withdrawal

Note that the specific questions and choice sets that are included in this protocol 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.

6 Statistical Analysis

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). The primary evaluation will be the assessment of cefepime pharmacokinetics. Data from all subjects will be included in the analysis. Pharmacokinetic samples will be obtained from indwelling catheters or the ECMO circuit. Plasma concentrations of cefepime will be determined using a validated

high performance liquid chromatography - tandem mass spectroscopy method developed in the laboratories of the Division of Clinical Pharmacology at The Children's Hospital of Philadelphia.

In this pilot study, initial efforts will be to design a suitable PK model to fit plasma concentrations using nonlinear mixed-effects modeling as implemented in the program NONMEM (version VI, ICON Development Solutions, Ellicott City, MD). This technique allows the estimation of inter-individual variability in PK parameters (CLs, volumes of distribution). Inter-individual variability for PK parameters will initially be assumed to follow a log-normal distribution, but other models may be employed as indicated by the data and diagnostics. Various models for residual variability (accounting for measurement noise, model mis-specification, within-subject variability, and errors in sampling times) may be evaluated, including log-normal, proportional and combined additive/proportional model. Initial modeling efforts will employ the first-order conditional estimation method, but other methods, such as stochastic expectation-maximization and full Bayesian Markov Chain Monte Carlo may be employed, as needed. Model comparison and goodness of fit will be based on assessment of successful convergence of the estimation method, diagnostic plots, precision and plausibility of parameter estimates, and a goodness of fit statistic, such as AIC (or DIC for Bayesian methods).

After completion of the base model, a covariate model will be explored incorporating covariates such as weight, temperature, type of ECMO (VA vs. VV), and measures of renal and hepatic function. Initial attempts will be made to create a model that will describe cefepime disposition across all participating subjects. If this pilot study determines that the variability in cefepime disposition is too large (i.e., difference in drug clearance or volume of distribution of greater than 50%), this preliminary data will be used to perform clinical trial simulations to design a pharmacokinetic study that will adequately describe drug disposition in a full covariate model.

6.1 Sample Size

The cohort will be considered evaluable when:

- it contains at least 40 subjects; AND
- at least 30 subjects have 80% or more target PK samples obtained during the sampling period for at least one dose; AND
- at least 40 subjects have 50% or more target PK samples obtained during the sampling period for at least one dose.

Enrollment for the cefepime cohort will continue until there is an evaluable cefepime cohort, as defined above. To achieve an evaluable cohort, we may enroll more than 40 subjects. However, all subjects will be included in the analysis, regardless of the number of PK samples obtained.

7 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.

7.1 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). This system provides secure user access via the Internet, and maintains an audit log for all study events and data.

7.2 Data Security

The DCC is located at the University of Utah in Salt Lake City, Utah. The DCC has a state-of-the-art data center infrastructure with a dedicated security server facility with racks, inline cooling, uninterruptible power supply, high speed networking, security cameras, firewall protection, and 24/7 systems and security monitoring. 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 four 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 EDC system, 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.

7.3 Protection of Confidentiality

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

Plasma sample paperwork sent to CHOP will be kept in a locked filing cabinet in the investigator's locked office. In addition, all data will be deidentified prior to sending. Electronic data will be deidentified, and stored in a password protected computer. All data and records generated during this study will be kept confidential, and publications will not enable identification of individual subjects. These efforts will decrease the risk of loss of confidentiality.

7.4 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 subject protection requirements and assurance of high quality study data. Monitoring is done remotely.

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.

7.5 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.

8 Protection of Human Subjects

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

Informed Consent: The investigational nature and objectives of the study, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject's parents or guardian, and a signed informed consent will be obtained according to institutional guidelines. Subject assent will not be obtained as subjects will be unable to assent due to the nature of the illness and age.

Potential Benefits: There are no direct benefits of study participation. Participation will further the knowledge of cefepime PK during ECMO, and therefore, is an indirect benefit only.

Potential Risks: As this is primarily a PK study, and requires only blood sampling, risks attributable to this study are limited to central line associated bloodstream infections.

All efforts will be made to coordinate PK sampling with labs being drawn as standard of care from arterial/central lines to minimize the number of times an arterial/central line is accessed. The PK sampling scheme serves as a guide for PK sampling times, but will allow flexibility so that PK sampling can occur with scheduled labs. This will decrease the risk of central line associated bloodstream infections.

Protection Against Risks: If the site PI determines that it is not in the best interest of a child to undergo PK sampling, the child will be withdrawn from the study. All procedures are being carried out in critical care units with expert nursing and physician staff who are fully aware of sterile technique and methods to reduce central line infections.

9 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 offered Business Associate Agreements (BAAs) with the University of Utah. Copies of signed BAAs are maintained at the DCC.

In accordance with NIH requirements, a public use dataset will be made available after completion of the study. This database will be completely de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA).

10 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.

11 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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