Inhaled Nitric Oxide Use in Pediatric Intensive Care (Nitric Oxide)
CPCCRN Protocol Number 054

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

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PROTOCOL TITLE:

Inhaled Nitric Oxide Use in Pediatric Intensive Care

Short Title: Nitric Oxide
CPCCRN Protocol Number: 054

Lead Investigator and Author:
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Children's National Medical Center

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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

Acute lung injury (ALI) occurs in approximately 9% of mechanically ventilated children with 80% progressing to ALI's most severe form, acute respiratory distress syndrome (ARDS). Inhaled nitric oxide (iNO) is an important therapy for neonates with persistent pulmonary hypertension of the newborn, older children with pulmonary hypertension and patients with congenital heart disease. It has been hypothesized that iNO should benefit patients with ALI/ARDS by improving oxygenation and limiting ventilator and oxygen induced lung injury. Clinical trials, however, have not been able to prove this hypothesis.

Despite lack of proof of efficacy, iNO continues to be frequently used in pediatric ALI/ARDS. The continued use of iNO may be based on bias towards intervention and the perceived lack of toxic effects of iNO. Inhaled nitric oxide is variably used among the sites within the CPCCRN. In the recently published TOPICC study, 285 (2.8%) of the 10,078 enrolled subjects received iNO during the PICU admission, which represents $\approx$ 500 patients per year.

This study is a prospective observational cohort study, and its descriptive results will be used to inform the design and implementation of a randomized, controlled trial of iNO in pediatric intensive care (medical and cardiac).

1 Study Summary

1.1 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Characterize the use of iNO in children including indications, dose, and clinician responsiveness to change in patient oxygenation.

Specific Aim 2. Characterize outcomes of patients who receive iNO related to diagnostic group and clinician responsiveness including effects on gas exchange, ICU morbidities and mortality.

1.2 Hypotheses

The hypotheses of this study are:

1. Clinician responsiveness to an improvement in oxygenation from inhaled nitric oxide is associated with ventilator-free days, functional status, and ICU mortality.

2. Patient response to inhaled nitric oxide in ALI/ARDS varies between diagnostic groups.

1.3 Subject Eligibility, Accrual and Study Duration

Inclusion criteria are:

1. Age less than 18 years; AND
2. Mechanically ventilated; AND
3. Receives inhaled nitric oxide (iNO) in the PICU or CICU.

Exclusion criteria are:

1. The patient is a newborn with congenital diaphragmatic hernia; OR
2. The patient is a newborn with meconium aspiration syndrome; OR
3. The patient is a newborn with persistent pulmonary hypertension of the newborn; OR
4. Patient started on iNO at an outside institution; OR
5. Patient previously enrolled in this study within the same hospitalization.

The study is anticipated to enroll all eligible patients for one year. Based on other CPCCRN studies, it is expected that 400 to 500 subjects will be enrolled.

2 Rationale and Background

Acute lung injury (ALI) occurs in approximately 9% of mechanically ventilated children with 80% progressing to ALI's most severe form, acute respiratory distress syndrome (ARDS).[1] Inhaled nitric oxide (iNO) is an important therapy for neonates with persistent pulmonary hypertension of the newborn, older children with pulmonary hypertension and patients with congenital heart disease. While it has been hypothesized that iNO should benefit patients with ALI/ARDS by improving oxygenation and limiting ventilator and oxygen induced lung injury, limited clinical trials have not been able to prove this hypothesis.

Randomized control trials of iNO in pediatric and adult ALI/ARDS have shown acute improvements in gas exchange but have not shown to improve survival.[2–7] A meta-analysis of 14 randomized control trials including 3 pediatric trials with 1303 participants failed to show a statistically significant benefit of iNO on 28 day mortality with a relative risk of death of 1.12 (95% CI 0.93 to 1.31).[8] Subgroup analysis of the pediatric studies did not demonstrate a beneficial effect on mortality either.

The largest pediatric trial included 108 children who were randomized to iNO at 10 parts per million (ppm) or placebo for 3 days.[4] The primary endpoint was treatment

failure defined by one of three criteria, oxygenation index (OI) > 40 for 3 hours, OI > 25 for 6 hours, or hemodynamic deterioration. While iNO improved oxygenation, the number of treatment failures was not different between the 2 groups. Children with treatment failure could receive iNO after study exit, a trial design weakness which precluded a mortality assessment. Although patients were classified into diagnostic categories, the effects of iNO in the subgroups were not assessed except for immunocompromised patients. In immunocompromised patients, iNO treated patients had a sustained response (p=0.033) as did patients who had an initial OI > 25. Other important clinical markers such as the use of extracorporeal membrane oxygenation (ECMO), ventilator free days, or length of stay were not reported.

There are several possible explanations for the failure of iNO to improve survival in these studies. The benefits of iNO may have been overwhelmed by harmful mechanical ventilation practices, especially when considering the wide variability in ventilator management and use of other adjunctive therapies between centers.[9] Many of the trials were conducted before widespread adoption of low tidal volume lung protective strategies as advocated today.

In the pediatric trial of iNO, investigators agreed to general guidelines for mechanical ventilation incorporating an "open lung approach".[4] Treatment goals included a SaO2 > 90% with FiO2 < 0.6 and PaCO2 45-55 mmHg. Higher PaCO2 was tolerated if pH > 7.2. Attempts were made to limit PIP to < 35-40 mmHg. While the authors showed a decrease in OI with iNO, what is not clear is whether it changed related to changes in PaO2 or concomitant weaning of ventilation. A post hoc analysis of the initial trial revealed a significant interaction between ventilator strategy, iNO use, and oxygenation. The authors compared the response to treatment with iNO during high frequency oscillatory ventilation (HFOV) versus conventional mechanical ventilation (CMV).[10] Patients (n=14) who were treated with iNO and HFOV had a greater acute improvement in oxygenation than those receiving CMV alone or CMV plus iNO as measured by PaO2/FiO2 ratio and OI. During prolonged treatment (72 hours), HFOV alone or with iNO resulted in greater improvement in oxygenation than CMV with or without iNO. This improvement along with a study of iNO in newborns suggests ventilator strategy plays an important role in determining the response to iNO.[11]

Other explanations for the failure of previous trials to demonstrate effectiveness include heterogeneous populations with ALI/ARDS. For example, the diverse etiologies of ARDS in the largest adult study included massive transfusion, trauma, and pneumonia.[7] There are suggestions that some diagnostic groups have a better response to iNO.[4] Additionally, iNO has been started at various time points after the development of ARDS with a suggestion that iNO is less effective in late stages of disease.[4] All pediatric patients with

ARDS treated in an open label study of early iNO use had a sustained response to iNO and a reduction in ventilator settings.[12] The large adult randomized trials have used fixed doses of iNO possibly undertreating patients and/or exposing others to possible toxic effects such as oxidative damage.[13] Finally, most patient deaths in ARDS are associated with multiple organ failure rather than refractory hypoxemia.[9, 14]

Despite these negative studies, iNO continues to be frequently used in pediatric ALI/ARDS. In a cross-sectional study that included 59 PICUs in 12 countries, iNO was used in 21 (12.7%) of patients with ALI.[15] Likewise in a recent randomized trial of surfactant, 14 of 110 subjects were treated with iNO.[16] This trial like other interventional trials in ALI/ARDS failed to show benefits in terms of survival or ventilator-free days. The continued use of iNO may be based on bias towards intervention and the perceived lack of toxic effects of iNO.

Trials in children with ALI/ARDS are challenging due to heterogeneous populations, infrequent mortality, variable use of adjunctive therapies, and short duration of mechanical ventilation.[15, 17] Children with acute lung injury and who can participate in a clinical trial are rare. A recent study conducted in 59 pediatric ICUs screened 3823 patients for ALI.[15] Diagnosis of the ALI required acute onset of hypoxemia, bilateral infiltrates on chest radiograph, no evidence of heart failure and a PaO2/FiO2 ratio < 300 torr. Only 165 children (4.3%) met all the inclusion and exclusion criteria for a clinical trial. These results mirror an early study where 6403 total ICU admissions were screened to find 395 (6%) children requiring ventilator support for > 24 hours who would be eligible for a study of acute respiratory failure.[17] Additionally, 43-75% of pediatric patients with ALI/ARDS have significant chronic underlying disease including heart disease, cancer and solid organ transplant.[15, 17] Consequently, ALI trials will require careful planning of outcomes and interventions to minimize recruitment periods, drift in clinical practice, and study fatigue.

Inhaled nitric oxide use is variably used among the sites within the CPCCRN. In the recently published TOPICC study, 285 (2.8%) of the 10078 enrolled subjects received iNO during the PICU admission.[18] The frequency of use varied among the sites with a range of 1 - 5.8% of the enrolled patients. These enrolled patients had higher rates of new morbidity 15.4% and mortality 16.8% than seen in the entire cohort which suggests that morbidity as assessed by the functional status scale may be a potential practical outcome.

Another challenge to a robust clinical trial is a use of mortality as an endpoint. Recent studies of pediatric ALI suggest a relatively low hospital mortality risk estimated between 8-35%.[9, 19–22] The study with the highest mortality included children treated in adult ICUs which may have affected outcome.[21] It was estimated in 1 study that it would take 4 years and at least 60 PICUs to enroll enough children with ALI/ARDS in a clinical trial using

a reduction in mortality as the primary endpoint.[15] Inhaled NO may have other benefits that could be elucidated in a clinical trial such as the reducing the long term sequelae of ALI/ARDS. In a study of 92 adult survivors of ALI, iNO use was associated with better pulmonary function tests at 6 months following disease onset.[23] Conversely, iNO does not appear to improve survival without bronchopulmonary dysplasia in preterm infants.[24, 25] Meta-analysis showed that iNO did not reduce duration of mechanical ventilation or increase ventilator free days in adults.[26] Other endpoints such as ventilator free days, length of mechanical ventilation, and functional status at hospital discharge have not been systematically evaluated in pediatric trials of iNO.

3 Significance

Acute lung injury and acute respiratory distress syndrome remain important disease in pediatric critical care. While there is a physiologic basis for iNO use, demonstrating its benefit in clinically important variables has been difficult using traditional variables like 28-day survival and ventilator free days. Further, there are suggestions of differences in responsiveness to iNO based on patient diagnosis, timing of clinical use and ventilator strategy. Seeking an understanding of variations in the indications and treatment strategies of iNO will provide vital data for planning a randomized control trial of iNO.

4 Study Design and Data Collection

4.1 Study Design Overview

This is an descriptive, observational study. Prospective observational data from CPCCRN pediatric ICUs will be analyzed to define clinically important endpoints for a randomized trial of iNO and to identify practice variations that would affect such a trial.

4.2 Participant Screening and Consent

Patients in the PICU and CICU will be screened on a daily basis to identify infants and children who are being treated with iNO; all identified patients will be entered into the study. Waiver of consent is requested as discussed in Section 7.2 on page 22.

4.3 Data Collection

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.

Day 0 (zero) begins at the time of iNO initiation until the end of the calendar day, and days 1 to 28 will be based on calendar days. Daily data will be collected through study day 28, death, or discharge from the ICU, whichever occurs first.

4.3.1 Baseline Data Obtained on Enrollment

Demographics.

- Date of birth
- Gender
- Ethnicity
- Race

Admission Information.

- Hospital Admission date and time
- ICU Admission date and time
- ICU type (Medical, Surgical, Cardiac, or other)
- Postoperative cardiac surgery admission (Y/N)
- Postoperative cardiac catheterization admission (Y/N)
- Date and time of mechanical ventilation initiation
- Baseline Functional Status Score

Was there a history of prematurity (< 37 weeks gestation at birth)? Y/N
If yes, then enter the birthweight (grams) and the estimated gestational age (weeks).

Acute Diagnosis Information.

- Primary organ system dysfunction leading to iNO initiation (Respiratory OR Cardiac, not both)
  - Respiratory (Select primary from below)
    - Asthma
    - Bronchiolitis - Not RSV
    - Pneumonia - Aspiration
    - Pneumonia - Bacterial
    - Pneumonia - Viral other than RSV
    - RSV - pneumonia/bronchiolitis/pneumonitis
    - Acute lung injury - sepsis
    - Acute lung injury/ARDS non pulmonary etiology
    - Pertussis
  - Cardiac (Select primary from below)
    - Congenital Heart Disease
    - Heart Transplant - Post Operative
    - Cardiomyopathy

* Cardiomyopathy - s/p ECMO or VAD placement
* Pulmonary Hypertension - Chronic (not post surgical)

Chronic Diagnoses. Select all of the following that are applicable to this patient:

- Asthma
- Cancer
- Cardiovascular disease - acquired
- Cardiovascular disease - arrhythmia
- Cardiovascular disease - congenital
- Chronic renal failure
- Chronic lung disease of Infancy (BPD)
- Chronic lung disease - other (e.g.CF)
- Chromosomal Defect
- Connective tissue Disease
- Diabetes
- HIV
- Hypercoaguable Disorder
- Liver Disease
- Musculoskeletal
- Neurologic - static encephalopathy
- Neurologic - Other chronic condition
- Neurologic - Chronic seizures
- Obesity - Morbid
- Obstructive Sleep Apnea
- Prematurity
- Sickle Cell Disease
- Transplant - Solid Organ
- Transplant - Bone Marrow
- Other (Specify)

If patient has congenital heart disease, select all of the following that are applicable:

- Anomalous coronary artery
- Anomalous pulmonary venous return (partial)
- Anomalous pulmonary venous return (total)
- Aortic insufficiency
- Aortic stenosis (atresia)
- Atrioventricular canal defect
- Atrial septal defect (primum)
- Atrial septal defect (secundum)
- Coarctation of the aorta

- Cor triatriatum
- Double outlet right ventricle
- Ebstein's anomaly
- Hypoplastic aortic arch
- Hypoplastic left heart syndrome
- Interrupted Aortic Arch
- Mitral insufficiency
- Mitral stenosis
- Patent ductus arteriosus
- Pulmonary atresia
- Pulmonary valve or artery stenosis
- Pulmonary Vein Stenosis
- Single ventricle (not hypoplastic left heart syndrome)
- Tetralogy of Fallot
- Transposition of the great vessels
- Tricuspid stenosis/atresia
- Truncus arteriosus
- Ventricular septal defect
- Other cyanotic heart disease (specify)
- Other non-cyanotic heart disease (specify)

If patient has acquired heart disease, select all of the following that are applicable:

- Arrhythmia
- Cardiac arrest
- Cardiomyopathy
- Congestive heart failure
- Kawasaki's disease
- Myocarditis
- Overdose with cardiac affects
- Rheumatic fever
- Supraventricular tachycardia
- Transplant rejection
- Tumor
- Vasculitis
- Other (Specify)

Information concerning pre-existing (chronic) pulmonary hypertension:

- Pre-ICU diagnosis of pulmonary hypertension? (Y/N)
- If yes, was patient receiving treatment for pulmonary hypertension?
- If yes, identify the treatment from list below.

Therapies for pulmonary hypertension include epoprostenol, trespostinil, iloprost, beraprost, bosentan, ambrisentan, macitentan, sitaxentan, sildenafil, tadalafil, riociguat.

Technology Dependence. Indicate if patient was dependent on any of the following prior to hospitalization:

- Oxygen
- Tracheostomy
- Home/Chronic ventilator
- Chronic vascular access

4.3.2 Nitric Oxide Initiation (Day 0)

- Was the patient on CVVH/dialysis at the time of iNO initiation? (Y/N)
- Was the patient on ECMO at the time of iNO initiation? (Y/N)
- Did the patient have a cardiac arrest in the 12 hours prior to iNO initiation? (Y/N)
- Was iNO initiated after cardiac catheterization? (Y/N). If yes, upload full report.
- Was iNO initiated after cardiac surgery? (Y/N). If yes, indicate if the patient had any of the following:
  - Bidirectional Glenn procedure or Hemi-Fontan (Y/N)
  - Fontan (Y/N)
  - Heart transplant (Y/N)
  - Ventricular assist device placement (LVAD, RVAD, single ventricle) (Y/N)
- Was an echocardiogram obtained prior to iNO initiation? (Y/N). If yes, upload full report.

If echocardiogram was obtained, abstract the following data from the full report:

- TR velocity
- Septal motion
- RV function
- RV size
- PA size
- LV function

Was invasive measurement of pulmonary artery pressure performed prior to initiation of iNO? (Y/N) If yes, record PA systolic, PA diastolic, PA mean pressures and simultaneous systemic pressures.

Primary indication for initiation of iNO (only ONE):

- Acute hypoxemic respiratory failure without elevated PA pressure
- Acute hypoxemic respiratory failure with documented elevated PA pressure
- Postoperative cardiac surgery pulmonary hypertension

- Pre-existing chronic pulmonary hypertension
- Other (specify)

Initation information:
- Location where iNO was initiated (PICU, CICU, cardiac OR, other OR, catheterization lab, ER)
- Date and time of initiation of iNO
- Initial dose of iNO

4.3.3 Respiratory data for first 48 Hours of iNO

Blood gas data consists of date, time, FiO_2, pH, pCO_2, pO_2, and CO-oximeter saturation.

Conventional mechanical ventilator data include date, time, mode, mean airway pressure, PIP, PEEP, FiO_2, rate, tidal volume, $EtCO_2$, and the pulse oximeter saturation immediately before the ventilator setting was made.

High frequency oscillatory ventilator data include date, time, mean airway pressure, amplitude, frequency, FiO_2, and the pulse oximeter saturation immediately before the oscillatory ventilator setting was made.

The blood gas and ventilator settings just prior to iNO initiation should be recorded. After iNO is initiated, all ventilator changes and all arterial blood gas data should be recorded through 48 hours of study participation. In addition, the pulse oximeter saturation should be recorded every hour for the 48 hours, and if available, $EtCO_2$ should be recorded every hour for the 48 hours.

4.3.4 Nitric oxide log for first 48 hours

All iNO dose changes should be recorded for 48 hours. These data will be in a log form, and will include the date and time of the dose change, the dose before the change, the dose after the change, and the FiO_2 before the dose change.

4.3.5 Daily Data

These data should be collected every day for all study days through day 28. Obviously, death or discharge may occur prior to 28 days, in which case daily collection will end.

Morbidity events. Indicate yes or no to all of the following:

- ECMO initiated (y/n)
- HFOV initiated (y/n)
- CVVH/Dialysis Initiated (y/n)
- Cardiac Arrest (y/n)
- Was the patient on mechanical ventilation today? (y/n)
- Was the patient continuously on iNO today?
- Was the patient discontinued from iNO today?
- Was the patient restarted on iNO today?
- Did the patient receive sildenafil or tadalafil today?
- Was an echocardiogram performed today? If yes, upload report.
- Was a cardiac catheterization performed today? If yes, upload report (which may not be available for 1 to 2 weeks after procedure.)

If echocardiogram was obtained, abstract the following data from the full report:

- TR velocity
- Septal motion
- RV function
- RV size
- PA size
- LV function

4.3.6 Summary Final Data

A log form should be created for the endotracheal intubation and extubations; this should include date and time of intubations and extubations. The first entry should be the same as the date and time of mechanical ventilation initiation noted in the admission information. The last entry should be the date and time of final extubation and separation from mechanical ventilation. If the child has chronic ventilatory support, use date of return to pre-admission ventilator settings.

- Vital status at 28 days: alive or dead. If discharged from hospital prior to 28 days, assume alive.
- ICU discharge date and time.
- Hospital discharge (or death) date and time.
- Vital status at hospital discharge (alive or dead)
- Functional status score at ICU discharge or 28 days, whichever occurs first

5 Data Analysis

The hypotheses of this study are:

1. Clinician responsiveness to an improvement in oxygenation from inhaled nitric oxide is associated with ventilator-free days, functional status, and ICU mortality.

2. Patient response to inhaled nitric oxide in ALI/ARDS varies between diagnostic groups.

5.1 Specific Aim Analyses

Specific Aim 1. Characterize the use of iNO in children including indications, dose, and clinician responsiveness to change in patient oxygenation.

This Aim will involve descriptive reporting of iNO use including indications, dose and clinician responsiveness as well as variation in practice across CPCCRN sites.

Clinician responsiveness will be assessed from plots of iNO dose, MAP, FiO_2, pO_2, $EtCO_2$generated from the hourly data. Graphs will be adjudicated by investigator committee to assess clinical team responsiveness. Minimum parameters for responsiveness include a reduction in $FiO_2$to 0.6 or less with an oxygen saturation greater than 88% (excluding patients with cyanotic heart disease). Patients who had iNO initiated while on ECMO will be analyzed separately.

Specific Aim 2. Characterize outcomes of patients who receive iNO related to diagnostic group and clinician responsiveness including effects on gas exchange, ICU morbidities and mortality.

This Aim is exploratory and will include assessment of associations of various factors as listed in the data collection section above with patient outcomes.

6 Data Management

6.1 CPCCRN Data Coordinating Center (Utah)

In addition to locally secured, identifiable information, partially identifiable information for all sites will be maintained at the CPCCRN Data Coordinating Center, located at the University of Utah in Salt Lake City, Utah.

6.1.1 Facility, Hardware, Storage, Data Backup and System Availability

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 of 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 will 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. Our storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

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

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

6.1.2 Security, Support, Encryption 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.

The investigators and staff of the Data Coordinating Center are fully committed to the security and confidentiality of all data collected for CPCCRN studies. All Data Coordinating Center 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 staff, reviewers and investigators involved with this study will be required to sign agreements from the Data Coordinating Center that relate to maintenance of passwords, information system security, and data confidentiality.

6.2 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 usually done remotely and may also involve physical site monitoring visits. Site monitoring is described in more detail in Section 8.2.

6.3 Record Access

The medical record and study files (including informed consent, permission, and assent documents) 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 of the the National Institutes of Health, Food and Drug Administration, and the Institutional Review Board (IRB) for each study site.

7 Protection of Human Subjects

7.1 Institutional Review Board (IRB) Approval

The Data Coordinating Center and each clinical center must obtain approval from their respective IRB prior to participating in the study. The Data Coordinating Center 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.

7.2 Informed Consent

Since the study design is a daily review of existing information in the medical record and carries minimal risk to the patient, waiver of informed consent is requested. The scientific validity of this study requires completely unbiased enrollment of subjects, as the study is evaluating the utilization of iNO in current practice.

7.3 Potential Risks

There is a minor risk of loss of confidentiality.

7.4 Protections Against Potential Risks

Loss of confidentiality will be mitigated by the use of the CPCCRN Data Coordinating Center which has a highly secure IT infrastructure, and by the existence of trained research staff at participating sites. Data security is described in Section 6.

7.5 Potential Benefits

The results of this study may benefit the management of future infants and children by providing necessary data to design and implement a randomized, controlled trial of iNO for respiratory failure.

8 Study Training and Monitoring

8.1 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, adverse event reporting, data entry procedures, quality assurance, site

monitoring, and the waiver of informed consent. A manual of operations will be provided to each Clinical Center investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, 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. Berger), will be the main contact for study questions.

8.2 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 the proposed study. Our 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.

8.2.1 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol will be completed which outlines specific criteria for 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.

8.2.2 Clinical Site Monitoring

Site monitoring visits may be performed, in which case they will be done by a trained site monitor during the study period to ensure regulatory compliance, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on risk assessment, grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will be limited due to the low risk of the observational design.

8.2.3 Remote Monitoring

The Data Coordinating Center may supplement on-site monitoring with remote monitoring activities. 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 data quality. This may require 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. 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 the documents will be retained in accordance with federal requirements.

9 Regulatory Issues

9.1 Health Insurance Portability and Accountability Act

The abstracted data will include limited identifiers as defined by the Health Insurance Portability and Accountability Act (birthdates and dates of service). Abstracted data will be retained and archived at the Data Coordinating Center in accordance with record retention requirements for Federally funded research. For data analysis outside the Data Coordinating Center (e.g., when a public access database is made available), the Data Coordinating Center 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 with the University of Utah. Copies of signed Business Associate Agreements are maintained at the Data Coordinating Center.

9.2 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 CPCCRN site participating in this trial. There will be no exclusion of patients based on gender, race, or ethnicity.

9.3 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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