

NICHD
NEONATAL RESEARCH NETWORK

Solicitation

Request for Proposal (RFP) Number:	NRN-Milrinone-2021-01
Title:	Clinical Sites to Recruit Participants into the Milrinone in Congenital Diaphragmatic Hernia Trial
Issued by:	RTI International (on behalf of the NRN) 3040 Cornwallis Road Research Triangle Park, NC 27709
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Submit Offers via:	https://neonatal.rti.org

The dates above may be modified at the discretion of the Issuer. Any changes or clarifications will be published in an amendment to this RFP and posted on the website listed above.

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SECTION 1. SUMMARY AND BACKGROUND

1.1. SUMMARY

RTI International (RTI), the Buyer, acting on behalf of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) under cooperative agreement number U24 HD95254, is soliciting offers from clinical sites in the United States to recruit patients and implement the NRN's Milrinone in Congenital Diaphragmatic Hernia trial ([NCT02951130](https://clinicaltrials.gov/ct2/show/study/NCT02951130)). This solicitation is for this trial only, not for participation in other NRN activities.

Independently and not as an agent of the Government or the NRN, the Contractor shall be required to provide all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the NRN, as needed to perform the Statement of Work. Services will support the conduct of the trial and the reporting of results in a timely fashion and in compliance with all applicable local, state, and Federal regulations and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

1.2. BACKGROUND

1.2.1. The Neonatal Research Network

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) established the Neonatal Research Network (NRN) in 1986 to perform interventional and observational clinical studies in newborn infants, particularly low birth weight infants. The NRN's objective is "to facilitate the advancement of neonatal care by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, can study the required numbers of patients and can provide answers more rapidly than individual centers acting alone."

The infrastructure is set up for randomized control trials and comparative effectiveness management trials with the ability to follow short-term (clinical effect) and long-term (general health and neurodevelopmental outcome) measures. The infrastructure is also set up for observational, longitudinal studies in the neonatal intensive care unit setting. In the current cycle, the NRN comprises 15 academic institutions, encompassing 32 hospitals/hospital systems plus a data coordinating center (DCC), operated by RTI International. As of January 2021, it has completed, or is currently implementing, 24 observational studies and 43 interventional trials. Details on current trials are available at <https://Clinicaltrials.gov> and at the NRN website: <https://neonatal.rti.org>. Details for the current Clinical Center Request for Applications (RFA) is available at <https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-16-020.html> and for the current Data Coordinating Center RFA is available at <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-13-014.html>. RTI International is the current NRN Data Coordinating Center (DCC).

1.2.2. The NICHD Strategic Plan 2020

In 2019, NICHD leadership provided a new Strategic Plan 2020 which provided four 'Guiding Principles' for the evolution of NICHD-supported clinical trial infrastructure. The supported infrastructure should:

1. Enhance rigor and reproducibility;
2. Promote greater availability of infrastructure;
3. Facilitate data sharing and access to biospecimens; and
4. Facilitate greater involvement of diverse populations in clinical trials.

In the spirit of items 2 and 4 above, and to ensure that currently ongoing NRN trials can be completed within a reasonable timeframe and with inclusion of diverse populations, the NRN invites applications from non-NRN investigators and institutions willing to participate with the Network in the Milrinone in Congenital Diaphragmatic Hernia Trial.

1.3. THE MILRINONE IN CONGENITAL DIAPHRAGMATIC HERNIA TRIAL

Below is a brief description of the trial. The Milrinone trial protocol is available at:

<https://mhnjournal.biomedcentral.com/articles/10.1186/s40748-017-0066-9>.

1.3.1. Study Background

Infants with congenital diaphragmatic hernia (CDH) usually have pulmonary hypoplasia and persistent pulmonary hypertension of the newborn (PPHN) leading to hypoxemic respiratory failure (HRF) that is often associated with cardiac dysfunction. Pulmonary hypertension associated with CDH is frequently resistant to conventional vasodilator therapy, including inhaled nitric oxide (iNO). Increased pulmonary vascular resistance (PVR) can lead to right ventricular overload and dysfunction.^{1,2} In patients with CDH, left ventricular dysfunction, either caused by right ventricular overload or a relative underdevelopment of the left ventricle, is associated with poor prognosis. Right ventricular dysfunction in CDH is also associated with poor prognosis.³

In many centers, milrinone is commonly used during the management of CDH, although no randomized trials have been performed to test its efficacy. Milrinone is an intravenous inotrope and lusitrope (enhances cardiac systolic contraction and diastolic relaxation respectively) with pulmonary vasodilator properties and has been shown anecdotally to improve oxygenation in

¹ Patel, N. (2012). Use of milrinone to treat cardiac dysfunction in infants with pulmonary hypertension secondary to congenital diaphragmatic hernia: a review of six patients. *Neonatology* 102(2): 130-136.

² James, A. T., et al (2015). The effect of milrinone on right and left ventricular function when used as a rescue therapy for term infants with pulmonary hypertension. *Cardiol Young* 26(1): 90-99.

³ Moenkemeyer, F. and N. Patel (2014). Right ventricular diastolic function measured by tissue Doppler imaging predicts early outcome in congenital diaphragmatic hernia. *Pediatr Crit Care Med* 15(1): 49-55.

PPHN.^{4,5,6,7} Thirty percent of infants with CDH in the Children's Hospital Neonatal Database (CHND)⁸ and 22% of late-preterm and term infants with CDH in the Pediatrix database⁹ received milrinone. In the recently published VICI trial, 84% of patients with CDH received a vasoactive medication.¹⁰

1.3.2. Study Objectives

This is a Phase II pilot trial to determine if milrinone infusion in neonates ≥ 36 weeks' postmenstrual age (PMA) at birth with CDH would lead to an increase in PaO₂ with a corresponding decrease in OI (or OSI) by itself or in conjunction with other pulmonary vasodilators such as iNO at 24 hours post-infusion. (Note: oxygenation index (OI), = Mean airway pressure x FiO₂ x 100 ÷ PaO₂ and oxygen saturation index (OSI) = Mean airway pressure x FiO₂ x 100 ÷ preductal SpO₂).

As secondary objectives, we will determine if milrinone improves oxygenation at 48 hours and 72 hours post-infusion, reduces right ventricular pressures on echocardiogram, and alters the risk of systemic hypotension, arrhythmias, intracranial hemorrhage, need for extracorporeal membrane oxygenation (ECMO), and chronic lung disease (CLD, defined as oxygen need at 28 days of postnatal age).

1.3.3. Study Design

This is a double-blind, randomized controlled pilot trial with 1:1 (treatment: control) randomization.

Eligibility criteria. Infants are eligible if they meet all of the following criteria:

- i. ≥ 36 0/7 weeks postmenstrual age at birth by best obstetric estimate AND birth weight of ≥ 2000 g
- ii. Postnatal age ≤ 7 days (168 hours of age, including post-operative infants with HRF)
- iii. Invasive mechanical ventilation (defined as ventilation with an endotracheal tube)
- iv. One arterial blood gas with an OI ≥ 10 (after tracheal tube obstruction, pneumothorax and other easily resolvable mechanical causes for increased OI are ruled out) on the most recent arterial blood gas within 12 hours prior to the time of randomization.

⁴ Bassler, D., et al (2006). Neonatal persistent pulmonary hypertension treated with milrinone: four case reports. *Biol Neonate* 89(1): 1-5.

⁵ McNamara, P. J., et al (2006). Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. *J Crit Care* 21(2): 217-222.

⁶ Bassler, D., et al (2010). Milrinone for persistent pulmonary hypertension of the newborn. *Cochrane Database Syst Rev* 10(11): CD007802.

⁷ McNamara, P. J., et al (2012). Pharmacology of Milrinone in Neonates with Persistent Pulmonary Hypertension of the Newborn and Suboptimal Response to Inhaled Nitric Oxide. *Pediatr Crit Care Med*.

⁸ Grover, T. R., et al (2015). Short-Term Outcomes and Medical and Surgical Interventions in Infants with Congenital Diaphragmatic Hernia. *Am J Perinatol* 32(11): 1038-1044.

⁹ Malowitz, J. R., et al (2015). Management Practice and Mortality for Infants with Congenital Diaphragmatic Hernia. *Am J Perinatol* 32(9): 887-894.

¹⁰ Snoek, K. G., et al (2016). Conventional Mechanical Ventilation Versus High-frequency Oscillatory Ventilation for Congenital Diaphragmatic Hernia: A Randomized Clinical Trial (The VICI-trial). *Ann Surg* 263(5): 867-874.

- v. If an arterial blood gas is not available at the time of randomization, a preductal OSI of ≥ 5 can be used as an inclusion criterion instead of $OI \geq 10$; (the OSI should be based on the most recent preductal pulse oximetry recording and must be within 12 hours of randomization)
- vi. Postnatal blood gas with $PCO_2 \leq 80$ mmHg (arterial, capillary, or venous blood gas) on the most recent blood gas sample obtained within 12 hours prior to randomization.

Note: Criteria (iv) to (vi) must be met at the most recent analysis within 12 hours prior to randomization.

1.3.4. Study Intervention/Methods

An initial cranial ultrasound is obtained prior to initiation of study drug or within 4 hours of commencement of the study drug. A second cranial ultrasound is obtained preferably within 24 hours (maximum - within 96 hours) of completion of the study drug. Both these cranial ultrasounds are covered by the study budget. Additional head imaging may be performed based on clinical indications (but are not covered by the study budget).

An echocardiogram, if clinically indicated, will preferably be obtained prior to (or within 6 hours of) initiation of the study drug.

Infants with CDH will be randomized to receive a milrinone infusion at $0.33 \mu\text{g}/\text{kg}/\text{min}$ or equal volume of placebo (D5W) infusion. The dose of the study drug will be increased to $0.66 \mu\text{g}/\text{kg}/\text{min}$ 2 to 4 hours after initiation of study drug, if there is no evidence of hypotension (as defined as mean blood pressure < 35 mmHg and a vasoactive inotrope score > 30 ; Vasoactive Inotrope score = dose of dopamine in $\mu\text{g}/\text{kg}/\text{min}$ + dose of dobutamine in $\mu\text{g}/\text{kg}/\text{min}$ + $100 \times$ epinephrine dose in $\mu\text{g}/\text{kg}/\text{min}$ + $100 \times$ norepinephrine dose in $\mu\text{g}/\text{kg}/\text{min}$ + $100 \times$ phenylephrine dose in $\mu\text{g}/\text{kg}/\text{min}$ + $10000 \times$ vasopressin dose in $\text{U}/\text{kg}/\text{min}$) two hours after initiation of study drug.

Infusion will be continued until the OI decreases to < 7 (or OSI < 3.5 , if no arterial blood gas is available). The study drug will be continued during surgery and if the patient requires either veno-arterial or veno-venous extracorporeal membrane oxygenation (VV-ECMO or VA-ECMO), if permitted by the clinical team. The maximum duration of study drug infusion is 72 hours. After 70 hours (if the patient is on $0.66 \mu\text{g}/\text{kg}/\text{min}$ or 72 hours if the patient is on $0.33 \mu\text{g}/\text{kg}/\text{min}$) of study drug infusion (or earlier if two consecutive OIs at least one hour apart are < 7 or OSIs < 3.5 if no arterial blood gas is available), the infusion rate of the study drug is weaned and subsequently discontinued.

Data will be recorded from a maximum of 4 echocardiograms, if performed for clinical indications:

1. Prior to onset of study drug (preferable) or within 6 hours of initiation of study drug
2. 6-36 hours after initiation of study medication
3. 36 hours after initiation of study medication, but prior to completion or discontinuation of study-drug, and
4. After completion of the study drug.

Infusion of the study drug will be stopped if the mean blood pressure decreases <35 mmHg and by >20 mmHg (from pre-study drug mean blood pressure) after initiation of study drug and remains low for 2 hours despite treatment with >40 ml/kg/24h of fluids and vasoactive medications (with a vasoactive inotrope score of >30). Once the study drug is discontinued for improvement in oxygenation or a decrease in systemic blood pressure, it will not be restarted even if the condition leading to discontinuation changes (such as change in oxygenation or blood pressure). However, clinical providers can initiate open-label milrinone at their discretion. Study drug will also be stopped in the presence of renal dysfunction and/or development of a large intracranial (intraventricular with distension of the ventricle or parenchymal) bleed/echodensity.

1.3.5. Study Follow-up

Infant's medical (pulmonary and nutritional) status will be evaluated at discharge and via telephone questionnaires at 4, 8, and 12 months of age.

1.3.6. Primary Outcome

The primary outcome is the oxygenation response, as determined by change in OI (or OSI if no arterial blood gas is available) at 24 hours after initiation of study drug. In patients that require ECMO or die prior to completion of 24 hours from the initiation of the study drug, the last OI (or OSI if no arterial blood gas is available) prior to initiation of ECMO or death will be used for analysis. In patients without an arterial line (or if the line is lost), oxygen saturation index (OSI) will be calculated using a preductal oximeter.

SECTION 2. STATEMENT OF WORK

2.1. SCOPE OF WORK

The objective of this contract is to:

- Recruit, consent, and randomize infants into the trial, following the protocol and manual of operations, as amended.

2.2. DELIVERABLES

Deliverables under this contract will include:

1. Initial IRB approval(s). Contractors will not be given access to the data management system until all required IRB approvals are submitted to RTI. The informed consent form must contain language informing participants that their data will be put into a database consisting of information from all of the participants in the study, and that data will be shared with other Network investigators, the study sponsor(s), and applicable federal agencies. In addition, data from the study may be shared with researchers outside of the Network, including depositing de-identified datasets in NIH-approved public databases. The consent form must be reviewed and approved by the DSMC before sites can start recruiting.
2. Training and certifications. The Site Principal Investigator, Coordinators, and Research Pharmacist must complete the required protocol and pharmacy trainings before recruitment can begin.
3. Recruitment, consent, randomization, and study drug administration of eligible study participants. Contractors will be paid on a per-patient basis for each participant randomized, once required data has been submitted via the study data management system. In some instances, a participant may be consented, but later becomes ineligible for the study prior to study drug administration. In these cases, a smaller capitation amount may be earned. Trial data will be entered via an online data management system set up by RTI. The Contractors will be provided training in how to use the system.
4. Successful head ultrasound prior to/within 4 hours study drug initiation. Contractors will be paid per-patient for submission of data for a successful head ultrasound performed on each participant before study drug is first administered or up to 4 hours after it is first administered.
5. Successful head ultrasound within 24 hours post study drug initiation. Contractors will be paid per-patient for submission of data for a successful head ultrasound performed on each participant within 24 hours after study drug is first administered.
6. Follow-up Questionnaire at 4-months corrected age. Contractors will be paid per-patient for submission of data from the 4-month follow-up questionnaire to be conducted with the parents and/or guardians via telephone.
7. Follow-up Questionnaire at 8-months corrected age. Contractors will be paid per-patient for submission of data from the 8-month follow-up questionnaire to be conducted with the parents and/or guardians via telephone.

8. Follow-up Questionnaire at 12-months corrected age. Contractors will be paid per-patient for submission of data from the 12-month follow-up questionnaire to be conducted with the parents and/or guardians via telephone.

2.3. SPECIFIC TASKS TO BE PERFORMED

2.3.1. Study Regulatory Requirements

This study is being conducted under an Investigational New Drug (IND) exemption from the U.S. Food and Drug Administration (IND 133502).

The NRR's Data and Safety Monitoring Committee has reviewed the protocol, and will continue to monitor the study for safety and feasibility issues.

Each Contractor shall obtain and maintain approval from an accredited Institutional Review Board (IRB) to participate in this study.

Within 24 hours of discovering a serious adverse event, per the study manual of operations, the Contractor will report the event to the NICHD, the Data Coordinating Center, and their own IRB per local requirements. A MEDWATCH form (FDA form 3500A) will be completed and submitted via email within 24 hours of the site being made aware of the event. RTI International will be responsible for any required reporting to the FDA.

2.3.2. Training and Certifications Requirements

Site investigators, coordinators, the research pharmacist, and other relevant personnel will be required to complete study-specific training.

2.3.3. Meeting Requirements

The site investigator and coordinator (or a designee) are also expected to participate in meetings/conference calls that are relevant to the specific protocol.

2.4. REPORTING REQUIREMENTS

2.4.1. Reporting of Financial Conflict of Interest (FCOI)

The Contractor must comply with the NIH Financial Conflict of Interest requirements for grantees. All reports and documentation required by 45 CFR Part 94, Responsible Prospective Contractors including, but not limited to, the New FCOI Report, Annual FCOI Report, Revised FCOI Report, and the Mitigation Report, shall be submitted to the RTI in electronic format. Details are available at: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-002.html> and <https://grants.nih.gov/grants/policy/coi/index.htm>. If the Contractor has already submitted relevant FCOI documentation to NIH, it may submit the filing and/or the website URL for its policy (required by the filing) to RTI. If the Contractor has not previously submitted a report to NIH, and does not have direct funding requiring it, it can submit similar documentation to RTI electronically.

Thereafter, reports shall be due in accordance with the regulatory compliance requirements in 45 CFR Part 94. Such reports may be forwarded to NIH/NICHD, as required.

If a FCOI exists, the NRN and NICHD will review the potential conflict and contractor amelioration plan to determine how seriously it might impact the study, the Network, and NICHD. Additional mitigation efforts may be required, if the proposed plan is deemed insufficient. RTI and NICHD reserve the right to cancel the contract or disqualify an Offeror if the conflict is considered serious, and/or the mitigation plan is unable to adequately minimize the risk.

45 CFR Part 94 is available at: <https://www.ecfr.gov/cgi-bin/text-idx?SID=054276802653319fa6cbd4f527ab5d23&mc=true&node=pt45.1.94&rgn=div5>. See Part 94.5, Management and reporting of financial conflicts of interest for complete information on reporting requirements.

2.4.2. Record Retention Requirements

Under this Contract, the Contractor must retain study records for at least 2 years after the primary paper has been published. Study records must be kept in either paper or accessible electronic format. Because Federal, state, and local requirements may require more extensive periods of retention, and these regulations are subject to change at any time, sites should check current regulations, including local requirements, before destroying any records.

2.4.3. Data Sharing Requirements

The NRN complies with the NIH Data Sharing Policy and the NIH Genomic Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm). The NIH policy states, “Data should be made as widely and freely available as possible while safeguarding the privacy of participants, and protecting confidential and proprietary data.” In addition, “Data sharing should be timely and no later than the acceptance for publication of the main findings from the final dataset. Data from large studies can be released in waves as data becomes available or as they are published.”

For data and biospecimens to be released, the informed consent forms for the specific study must contain language informing participating families that their child’s data will be put into a database consisting of de-identified information from all of the participants in the study, and that data will be shared with other Network investigators, the study sponsor(s), and applicable federal agencies. In addition, data from the study may be shared with researchers outside of the Network, including depositing de-identified datasets in NIH approved public databases.

Approval of requests for data, protocols, and other study materials is contingent on compliance with relevant local, state, and federal laws, such as those regarding intellectual property, and with Certificates of Confidentiality.

After this study is completed, data for the entire study will be stripped of identifying information and may be shared with outside researchers – including submitting de-identified data to the NICHD Data and Specimen Sharing Hub (DASH), the Database of Genotypes and Phenotypes (dbGaP), or other public databases, as appropriate.

SECTION 3. INSTITUTIONAL REQUIREMENTS

A preferred Application Template is available on the RFP website. *Please include the Application Checklist as the cover page to your proposal, even if you do not use the Application Template.* This page is not included in the page limits.

3.1. TECHNICAL REQUIREMENTS

3.1.1. Available Population

Please describe the site’s population and community served (e.g., race and ethnic diversity), recruitment location(s), and geographic catchment, including any overlap with existing Network sites (see <https://neonatal.rti.org/index.cfm?fuseaction=about.map> for awarded centers and their participating sites). Identify any special local, state, or tribal law governing human subjects’ oversight, based on population served.

To be considered for an award, **the offeror must have at least 10 infants per year** that meet the protocol eligibility criteria.

Please complete the table below as part of the Application Checklist cover page detailing the site’s available population. Where appropriate, please provide the most recent calendar year(s) for which data is available. If this proposal includes multiple recruiting sites, please provide a separate table for each site.

Hospital Name:	2018	2019	2020
Number of total NICU beds			
Number of NICU Admissions			
Number of CDH babies admitted ≥ 36 weeks GA at birth or ≥ 2000 g birth weight			
Number of CDH babies treated with ECMO			
Number of CDH babies who survived			

3.1.2. Recruitment Capabilities

Describe your site’s experience and ability to screen, recruit, and initiate study implementation 24 hours per day, 7 days a week, including holidays.

As part of this, an established electronic perinatal data system must be in place to collect and analyze patient information.

3.1.3. Ongoing Research at the Site

Describe any ongoing or upcoming research studies being conducted at the site(s) that may overlap with the proposed study population of infants with CDH. Please describe recruitment timing/procedures, study implementation procedures, and primary outcomes for these studies.

How will these studies fit with this Network protocol? The Network may need to review the protocol(s) prior to award to determine whether they conflict with the Network’s protocol.

Mothers enrolled in fetal tracheal occlusion studies, such as the Fetoscopic Endoluminal Tracheal Occlusion (FETO) study, may be enrolled if permitted by investigators of the study(ies).

Please note whether the site(s) are members of the CDH Registry, and for how long.

During recruitment for this NRN protocol, if the Site plans to initiate any new studies in this targeted population, the site will need to ask the NRN Concurrent Research Subcommittee to review the new study to see if it conflicts with the NRN protocol under this Contract.

3.1.4. Research-specific tests

The following research specific laboratory and other tests are required for this study on the schedule below. Please describe any special procedures you will need to put into place to conduct these tests in compliance with the protocol, taking into account that the timing of such tests may fall on holidays and/or weekends.

Test	Timing
Cranial ultrasounds	1) Prior to initiation of study drug or within 4 hours of study drug initiation 2) 24-96 hours after initiation of study drug
Echocardiograms (optional, but preferred; the study does not pay for ECHOs)	1) Just before study drug initiation 2) 6-36 hours after initiation of study drug 3) 36 hours to before completion of the study drug (typically a 72h infusion) and finally after completion of study drug.

3.2. STAFFING REQUIREMENTS

Sites must have adequate research and/or clinical staff to carry out the protocol screening, implementation, and adverse event monitoring and safety reporting, per the protocol and manual of operations. Applicants must provide a management plan delineating staff roles and responsibilities, how staff interact with subspecialists and senior/key persons (e.g., research pharmacists), and availability for staff to cover patient recruitment and study implementation at night and on weekends if required by the protocol.

3.2.1. Key Personnel

The Contractor shall identify at least the following key personnel in the proposal:

- Site investigator
- Alternate site investigator

3.2.2. Research Staff

The Contractor will provide the following research staff for the final Contract:

- Site investigator

- Alternate site investigator
- Research coordinator
- Data entry personnel

Please provide a NIH biosketch form for proposed personnel above in an appendix to your proposal. Details about this form are available at:
<https://grants.nih.gov/grants/forms/biosketch.htm>.

List the site's research staff, including anyone involved in consenting participants, monitoring and reporting adverse events, data collection, and chart abstraction. Data abstraction should be done by qualified medical personnel. Please include short 1-2 sentence biographies of research staff, their degrees/certifications, and their research experience.

The Site Investigator and Alternate Site Investigator should be practicing clinicians with prior experience conducting clinical trials in neonatology. Please describe their clinical, research, administrative and academic commitments in the NIH Biosketches. The Alternate Site Investigator must be able to serve in the absence of the Site Investigator.

The Research Coordinator should have at least 1 year of experience conducting clinical trials in the NICU, with multi-site trials experience preferred. Certified Clinical Research Coordinators® (CCRC) or equivalent are preferred. The Coordinator must have understanding of regulatory concepts and experience with protocol submission, amendments, and continuing review.

3.2.3. Staffing structure, roles, and responsibilities

The Site Investigator will have primary responsibility for:

- Developing and implementing strategies to conduct the protocol and meet recruitment goals.
- Collecting and transmitting the data to the DCC in an accurate and timely manner.
- Participating in analysis of the data and publishing results of the Network study.

As such, the site investigator's responsibilities include:

- Ensuring that the research is conducted in accordance with the study protocol, including all applicable federal regulations and guidelines, such as from the NIH, FDA, and OHRP.
- Obtaining and maintaining required Institutional Review Board (IRB) approvals, and ensuring that the necessary financial arrangements and federal assurances are in place before participation in, and during implementation of, the study. This includes submitting IRB approvals, continuing renewals, and other documentation to the DCC, and notifying NICHD and the DCC in a timely manner of any suspensions, changes, and other activities affecting study integrity and recruitment. This may also involve submitted any required documentation to cede institutional review to a central IRB.
- Notifying the DCC and NICHD Program Scientist of any serious adverse events, protocol deviations, and protocol violations in a timely manner.

- Ensuring collection and transmission of accurate data to the DCC in a timely manner. Chart abstractions must be done by qualified medical personnel to ensure accuracy of key primary and secondary outcome data.
- Participating in Network quality assurance efforts, including cooperating during site visits, responding promptly to data center inquiries, etc.
- Hiring and supervising qualified study personnel.
- Securing the cooperation of his/her institution and colleagues in Network research efforts.
- Communicating Network activities and issues to their research staff in a timely fashion, particularly those issues likely to affect the day-to-day operations of the protocol.
- Designating an alternate site investigator to act as the site investigator whenever the site investigator is not available. As acting, the alternate PI should have full authority to act in the site investigator's stead, including attending required Network meetings and/or teleconferences, voting on study subcommittee issues, and have the same access to the Network internal website.
- Notification to NICHD and the DCC of any staff changes in a timely manner.

The Research Coordinator, under the supervision of the site investigator, is responsible for:

- Assisting in the day-to-day operations of implementing the network protocol, including adhering to the protocol, collecting data, supervising data transmission, monitoring data quality, training staff, and procuring adequate equipment and supplies.
- Maintaining routine data quality assurance methods for staff under his/her supervision.
- Supervising data entry activities, including instructing and certifying data entry personnel in software and hardware usage, quality assurance of data entry, etc.
- Maintaining a central file of the protocol, manual of operations, data forms, regulatory documents, network correspondence, and performance reports in accordance with Good Clinical Practice (GCP).
- Collaborating with the site investigator and DCC in developing and revising (as needed) protocols, manuals of operation, and data collection forms.
- Attending Steering Committee meetings, the monthly Coordinator conference call, and meetings of any subcommittees of which they are a member, as needed.

Data Entry Personnel are responsible for: collecting completed data forms, entering data accurately into Network data management system(s), and transmitting the entries to the DCC in a timely manner.

Additional research staff may be needed to ensure coverage for protocol recruitment and/or implementation 24 hours per day, 7 days per week, including nights, weekends, and holidays, as needed for the protocol.

3.3. CORPORATE CAPABILITY REQUIREMENTS

3.3.1. Clinical Trial Research Experience

Does the offeror's neonatology department have experience conducting clinical trials in the NICU? What institutional research infrastructure is available to support the trial staff?

3.3.2. Research Office Space

Is there secure and dedicated research office space? Describe where it is located with respect to the Site Investigator's office, Labor and Delivery, and the NICU.

3.3.3. Investigational Drug Services / Research Pharmacy

This study is currently being conducted under an IND exemption.

Please review the protocol (available at:

<https://mhnjournal.biomedcentral.com/articles/10.1186/s40748-017-0066-9>) to ensure that the site will be able to implement the study procedures. The protocol spells out details of the milrinone/study drug drip preparation, including:

“Once the randomization code is received, the study pharmacist at the center will prepare an infusion of milrinone (pre-mixed bags containing 200 µg/mL of milrinone are preferred and do not need any further reconstitution in the pharmacy; Milrinone is also available in 1 mg/mL solution for injection as 10-, 20-, and 50-mL single dose vials).”

The study drug for this trial may need to be ordered and administered at nights and on the weekends. Please describe your site's experience and ability to provide 24/7 Investigational Drug Service/Research Pharmacy coverage, and a brief description of the planned pharmacy processes for your site.

3.3.4. Follow-up

For this study, please describe your site's ability to conduct phone interviews and follow-up patients at 4, 8, and 12 months of postnatal age.

3.3.5. Study oversight and IRB

Currently, this study is being conducted under local IRB oversight.

Please describe your site's planned oversight of study procedures and assurance of protocol adherence, especially during the first year by onsite personnel. Describe the site's institutional oversight of research, including IRBs and/or other committees (scientific, division, budgetary, nursing, or other review committees) with oversight. Describe the site's training processes prior to and post IRB approval.

3.3.6. Data collection and entry

Provide the plans for data handling (collection, entry, transmission, and quality control). Data abstractions should be done by personnel with a medical degree (BSN, RN, or higher).

3.3.7. Data quality assurance

Please include a detailed description of plans at the proposed site for quality assurance, monitoring data quality. How will accuracy of data entry be assured and data entry and updates (including screening logs) be tracked? Describe internal methods for data quality control and

assurance, as well as strategies for resolution of problems. Describe handling, timing, and resolution of edit corrections, data checks, and audits.

3.3.8. General Requirements of the Offeror

Organizations that submit proposals in response to this RFP must meet the following requirements:

1. Institutions and recruiting sites must be within the United States.
2. Companies or organizations, whether for-profit or non-profit, shall be requested to provide a DUNS number, if selected to receive a contract valued at USD\$30,000 or more, unless exempted.

Offerors may present their proposals as a member of a partnership with other institutions. In such cases, the contract will be awarded to the lead institution in the partnership, which shall be responsible for compliance with all contract terms and conditions and making all partnership arrangements, including but not limited to, division of labor, compliance monitoring, quality assurance, and invoicing, with the other entity(ies). A legally registered partnership is not necessary for these purposes; however, the different organizations must be committed to work together in the fulfillment of the contract terms. The proposals should describe the structure of the partnership and how activities will be coordinated and monitored.

SECTION 4. INSTRUCTIONS TO OFFERORS

Offerors are invited to submit proposals in response to this RFP in accordance with the Instructions to Offerors, which will not be part of the contract. The instructions are intended to assist interested Offerors in the preparation of their offer. Any resulting contract will be guided by this RFP.

This RFP does not obligate RTI, the NRN, NICHD, or the U.S. Government to execute a contract, nor does it commit these entities to pay any costs incurred in the preparation and submission of the proposals. Furthermore, RTI reserves the right to reject any and all offers, if such action is considered to be in the best interest of RTI, the NRN, and/or NICHD.

4.1. TYPE OF AWARD

RTI intends to issue multiple Fee-for-Service contracts under this RFP, managed by RTI International, on behalf of the NRN. RTI will establish a subcontract with each awardee and is responsible for establishing financial reimbursement systems. The Contractor is responsible for providing appropriate infrastructure to support the clinical trial requirements.

The Contractor shall be reimbursed in an amount not less than a total of \$0 (minimum) nor more than a total of \$65,000 cumulative amount over the period of performance (maximum) for successful performance of this contract.

While fixed rate subcontracts are anticipated, RTI reserves the right to issue one or more subcontracts of a different type.

4.2. PERIOD OF PERFORMANCE

The Period of Performance is from the date of contract award through March 31, 2023 or through trial completion, whichever comes first. Trial completion is the date of final data lock. The period of performance of any award(s) issued as a result of this RFP is subject to change.

4.3. OFFER DEADLINE

All offers must be received by the date and time listed on the RFP cover page, as amended.

Offerors are responsible for ensuring that their offers are received in accordance with the instructions stated herein. Late offers may be considered at the discretion of the NRN. RTI cannot guarantee that late offers will be considered.

4.4. WRITTEN QUESTIONS AND CLARIFICATIONS

All questions or clarifications regarding this RFP must be submitted in writing by the date and time listed on the RFP cover page. Questions and requests for clarification, the responses thereto, and any amendments to this RFP will be posted on the website for all potential offerors to see. It is the Offerors' responsibility to check for updates on that site. Only written

answers from RTI will be considered official and carry weight in the RFP process and subsequent evaluation. Any answers received outside the official channel, whether received verbally or in writing, from employees or representatives of RTI, the NRR, NICHD, or any other party, will not be considered official responses regarding this RFP.

4.5. INSTRUCTIONS FOR THE SUBMISSION OF ELECTRONIC COPIES

Offerors must be submitted electronically by uploading their documents via the website listed on the RFP cover page. The proposal and budget must be in Adobe Portable Document (PDF) format. Other files containing charts, graphs, and a complete protocol can be submitted in Microsoft doc, docx, rtf, txt or pdf. Offerors must not submit zipped files. Those pages requiring original manual signatures should be scanned and sent in PDF format; e-signatures are acceptable.

The technical proposal and cost proposal must be submitted in separate files from each other. Technical proposals must not make reference to pricing data, so that the technical evaluation may be made strictly on the basis of technical merit.

4.6. REQUIRED PROPOSAL DOCUMENTS

4.6.1. Cover Letter

The offeror's cover letter shall include the following information:

- Name of the institution
- Type of company or organization
- Name of the Signatory/Business Official
- Address
- Telephone
- Email
- Taxpayer Identification Number
- DUNS Number.

If Offeror does not have a DUNS number and is unable to obtain one before proposal submission deadline, the Offeror shall include a statement in their letter noting their intention to register for a DUNS number should it be selected as the successful offeror, or explaining why registration for a DUNS number is not possible. Contact Dun & Bradstreet through this webform to obtain a number: <https://fedgov.dnb.com/webform>.

If the offer is from a partnership or otherwise includes sub-sites, please include a letter from each organization stating its willingness to be included in the proposal.

In the cover letter, the offerors (and any partners) must clearly express their intent:

- To abide by the Network study protocol and provide the required staff, facilities, and equipment to comply with the protocol and all applicable federal, state, and local regulations and guidelines, such as from the NIH, FDA, and Office of Human Research Protection (OHRP).

- To participate in a cooperative manner with other NRN recruiting sites, the NICHD, and the NRN Data Coordinating Center in all aspects of the protocol research.
- To prioritize recruitment into the NRN protocol under this Contract, and during the time of the agreement with NRN not to initiate any new studies or trials that compete for enrollment in the same eligible population without prior approval.
- To cooperate with the policy for capitation of research costs and acceptance of protocol budgets for ongoing studies, including entering into a subgrant agreement with the DCC that flows down all NIH and other federal requirements for conducting federally funded clinical and human subjects research, including data sharing, and allows for payment of capitation.

4.6.2. Technical Proposal

Proposals should not exceed more than 10 pages (excluding the cover page, cover letter(s), and an appendix for biosketches) and provide enough information to judge institutional capabilities, experience, and expertise regarding the institutional requirements mentioned in Section 3. The technical proposal must respond to the detailed information set out in Sections 2 and 3 of this RFP, which provides the background, scope of work, and deliverables.

The technical proposal shall comprise the following parts:

- Application Checklist Cover Page. The template for this is in the Site Application Template available on the RFP website.
- Part 1: Technical Approach. This section should address the Technical Requirements described in Section 3 and the offeror's ability to conduct the planned research. This section should also propose milestones, including recruitment milestones for the study. This part may not exceed 5 pages.
- Part 2: Staffing. This section should address the Staffing Requirements described in Section 3. Offerors shall propose staff for the positions necessary for the implementation of the scope of work, and have the ability and flexibility to hire additional human resources, acting according to high standards in transparency and accountability. Biosketches or curriculum vitae should be included in an annex to the technical proposal and will not count against the page limit.
- Part 3: Corporate Capabilities, Experience, and Past Performance. This section should address the Corporate Capabilities Requirements described in Section 3. This part may not exceed 2 pages. Part 3 must describe the institution and any partner institutions/hospitals proposed for this Contract. Offerors must include details demonstrating their experience and technical ability in implementing the study.

4.6.3. Cost Proposal

The cost proposal is used to determine which proposals represent the best value and serves as a basis of negotiation before award of a contract.

Under no circumstances may cost information be included in the technical proposal. No cost information or any prices, whether for deliverables or line items, may be included in the technical proposal. Cost information must only be shown in the cost proposal.

Payments to the Contractor will be in the form of capitation payments per patient enrolled, plus applicable site indirect rates. Additional Other Direct Cost payments will cover:

- Study Start-up
- Pharmacy Start-up
- Pharmacy Maintenance Costs (annual payments every year after the first year)
- Protocol Training costs for the site investigator, coordinator, and other relevant personnel to attend a virtual training about the protocol procedures and data management system.
- Pharmacy Training costs for the research pharmacist and relevant personnel to attend a virtual pharmacy training

No additional base funding or infrastructure support will be paid.

Below are the fixed direct cost rates applicable to the Contract.

Cost Category	Rate
I. Capitation (includes night, weekend, & holiday coverage)	
A. Main Study	
Recruitment and implementation	\$1,590
Consented, but ultimately ineligible	\$240
Successful head ultrasound prior to/within 4 hours study drug initiation	\$300
Successful head ultrasound within 24 hours post study drug initiation	\$300
B. Follow-up	
Follow-up Questionnaire at 4-months corrected age	\$158
Follow-up Questionnaire at 8-months corrected age	\$158
Follow-up Questionnaire at 12-months corrected age	\$158
II. Material Costs	
Start-up activities	\$2,000
Pharmacy start-up costs	\$2,000
Pharmacy maintenance costs (per year after initial year)	\$500
Protocol training (virtual)	\$240
Pharmacy training (virtual)	\$240

The Offeror may propose different rates than those included in the table, but the Cost Proposal should indicate that the Site can conduct the study within the fixed direct cost rates listed in this RFP.

The Offeror should indicate the indirect rate(s) that should be applied to these fixed rates. If the site has a Negotiated Indirect Cost Rate Agreement (NICRA) with the Federal Government, it should provide a copy of it in a Cost Proposal appendix.

4.7. VALIDITY PERIOD

Unless extended, offerors' proposals must remain valid for 90 calendar days after the proposal deadline.

SECTION 5. EVALUATION CRITERIA

RTI will select the proposal(s) that offers the best value to the NRN and NICHD based upon the evaluation criteria stated in this RFP. RTI may award to a higher priced offeror if it is determined that the higher technical evaluation of that offeror merits the additional cost/price.

Offerors who are not excluded on the basis of not meeting the minimum requirements will be assessed on the basis of their score on the award criteria. This means that both the quality and price of the proposal will be taken into account.

5.1. APPLICATION REVIEW PROCESS

All applications received by the submission date/time will be evaluated by a Review Committee convened by NICHD. This committee will have representation from the NRN External Scientific Committee, DSMC, the Steering Committee Chair, and other external members (including possibly NICHD staff).

The Review Committee will complete all reviews within 6 weeks of the submission date. Applications receiving favorable reviews will be forwarded to the NRN Steering Committee and the Study Protocol Subcommittee for input and discussion. Final decisions on successful candidates will be made by NICHD in consultation with the DCC based on the quality of the applications received, Review Committee and NRN Steering Committee recommendations, and funding available.

5.2. SELECTION CRITERIA

Reviewers will consider the overall feasibility of adding the applicant as a single-trial site, and whether the conduct of the clinical trial will be productively enhanced and expedited by the addition of this site.

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact.

5.2.1. Overall Impact

Reviewers will provide an overall assessment of the likelihood for the applicant to successfully contribute to the execution of the concerned NRN trial, based on the following review criteria.

5.2.2. Technical Requirements (40 points)

- Is the eligible population available? Does the site meet the minimum number of eligible infants per year?
- Is the overall approach well-reasoned and appropriate to accomplish the site's integration with the NRN to implement this trial?

- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
- Are potential problems, alternative strategies, and benchmarks for success presented?
- Are the plans to address the protection of human subjects from research risks adequate?
- Is the organization approach appropriately designed to conduct the research efficiently?
- Are the plans for recruitment outreach, enrollment, retention, handling dropouts, and minimizing losses to follow-up appropriate to ensure robust data collection?
- Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate?
- Are the plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection or distribution guidelines appropriate?
- Is there a plan to obtain required study agent(s)?
- Does the application propose to use existing available resources, as applicable?

5.2.3. Staff Requirements (40 points)

- Are the site investigator, alternate site investigator, research coordinator, and other personnel well suited to the project? Do the proposed staff meet the minimum requirements for experience and certification. If Early Stage Investigators or those in the early stages of independent careers are proposed, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)?
- Do the investigators have complementary and integrated expertise; are their leadership approach, governance, and organizational structure appropriate for the project?
- With regard to the proposed leadership for the project, do the key personnel have the expertise, experience, and ability to organize, manage, and implement the proposed study and meet milestones and timelines?
- How strong is the Clinical Trial Experience of the personnel to conduct the proposed trial?
- How well-defined are the roles and responsibilities of the leadership?
- What evidence is provided to ensure that the site will employ the appropriate personnel to recruit subjects and design/implement the protocol?
- How strong is the project management expertise represented among the key personnel?
- How adequate are the descriptions of roles/responsibilities of the key personnel?

5.2.4. Corporate Capability Requirements (20 points)

- Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment, and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

- Does the application adequately address the capability and ability to conduct the trial at the proposed site(s)?
- Is there evidence of the ability of the , site , to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; (4) conducted required follow-up activities; and, (5) operate within the proposed organizational structure?
- Is there strong evidence that the institution has the available resources needed to conduct a randomized clinical trial?

5.2.5. Price criteria

Since any resulting Contracts will be based on the fixed rates detailed in this RFP, no separate points will be allocated for the Cost Proposal evaluation. As stated above, RTI will select the proposal(s) that offers the best value to the NRR and NICHD. This means that both the quality and price of the proposal will be taken into account for the Overall Impact criteria.

SECTION 6. AWARD ADMINISTRATION INFORMATION

6.1. AWARD PROCESS

Successful candidates will be invited by the DCC (acting on behalf of the NRN and NICHD) to begin negotiations no later than 12 weeks from the submission date. All official negotiations of the budget, terms, and conditions of any resulting Contract will be conducted between the Business Official of the lead Offeror and the DCC Subcontracts Specialist.

Best offer proposals are requested. It is anticipated that a contract will be awarded solely on the basis of the original offers received. However, RTI and the NRN reserves the right to conduct discussions, negotiations, and/or request clarifications prior to awarding a contract(s). Furthermore, RTI reserves the right to conduct a competitive range and to limit the number of offerors in the competitive range to permit an efficient evaluation environment among the most highly-rated proposals. Highest-rated offerors, as determined by the Review Committee, may be asked to submit their best prices or technical responses during a competitive range. RTI reserves the right to make separate awards per component, or to make no award at all.

All contracts, and major changes to contracts, particularly those resulting in substantive changes to the budget, require approval from the NICHD.

6.2. POST AWARD

Within two weeks of award receipt, the Contractor is expected to apply for IRB approval(s), provide the DCC with a final staffing plan and related contact information, and work with the DCC to schedule and record all necessary trainings and certifications of site staff slated to work on the study.

6.3. NEGOTIATIONS

The anticipated terms and conditions of any award issued as a result of this RFP are included as on the website noted in the RFP cover page.

6.4. TERMS OF CONTRACT

This is a request for proposals only, and in no way obligates RTI, the NRN, or NICHD to award a contract. In the event of contract negotiations, any resulting contract will be subject to and governed by the terms and clauses detailed in this RFP. Terms and clauses are not subject to negotiation. By submitting a proposal, offerors certify that they understand and agree to all of the terms and clauses contained in section III.

6.5. REJECTION OF SOLICITATION RESPONSE

RTI reserves the right to reject any or all responses received or any part thereof, to accept any response or any part thereof, or to waive any informalities when it is deemed to be in RTI's best interest.

6.6. CONFIDENTIAL INFORMATION

Notwithstanding any agreements, including any separate nondisclosure agreements, already in place between the parties, RTI assumes no obligation regarding confidentiality of all or any portion of a proposal or any other material except that RTI may not disclose any portion which the offeror clearly designates as containing proprietary information by affixing the legend "CONFIDENTIAL INFORMATION: Do not disclose" to the upper right-hand corner of each page of offeror's proposal which contains such proprietary information. The entire proposal or accompanying materials may not be marked as proprietary information. If the Offeror marks the entire proposal or accompanying materials as proprietary information, the parties agree that RTI shall be unduly restricted in its use of the proposal and materials, and therefore the parties agree that RTI may use, copy, and disclose any part of the proposal or materials except those which are clearly the proprietary information of the prospective supplier. In such event, RTI's sole responsibility shall be limited to maintaining the confidentiality of the information to the same extent that it maintains its own proprietary information.

6.7. PROHIBITION ON USE OF CERTAIN TELECOMMUNICATIONS AND VIDEO SURVEILLANCE SERVICES OR EQUIPMENT

In accordance with Section 889 of the John S. McCain National Defense Authorization Act for fiscal year 2019, RTI cannot use any equipment or services from specific companies, or their subsidiaries and affiliates, including Huawei Technologies Company, ZTE Corporation, Hytera Communications Corporation, Hangzhou Hikvision Digital Technology Company, and Dahua Technology Company ("Covered Technology"). In response to this request for proposals, please do not provide a quote which includes any Covered Technology. Any offer or proposal which includes Covered Technology will be deemed non-responsive.

Additionally, the Offeror shall not provide any equipment, system, or service that uses Covered Technology as a substantial or essential component under any resulting award.