



## REQUEST FOR PROPOSALS



**TITLE:** Additional Centers for the Sickle Cell Disease Clinical Research Network funded under NIH grant number U10HL083721

**RELEASE DATE:** September 2, 2008

### I. BACKGROUND

The Sickle Cell Disease Clinical Research Network (SCDCRN) is seeking to expand the number of research centers for participation in multi-center clinical studies over the remainder of its funding cycle (through March 31, 2011). The SCDCRN was established through a cooperative agreement (U-10) National Heart, Lung and Blood Institute (NHLBI) Request for Applications (RFA HL-05-006) and currently consists of eight clinical research centers, two patient outcomes cores, and a Data Coordinating Center (DCC), New England Research Institutes, Inc (NERI). Support for the SCDCRN included funds for the inclusion of additional sites as needed to complete clinical studies. Up to 12 additional clinical research centers will be added.

Initiation of at least two major studies is anticipated within the next 6 months which will require additional sites to achieve subject accrual goals:

PROACTIVE is a randomized controlled trial to determine if a single simple transfusion can reduce the incidence of acute chest syndrome in patients with sickle cell disease (all genotypes >2 years of age) hospitalized for pain crises. Hospitalized patients will be screened daily with a serum phospholipase A2 level to be established in the local laboratory to identify those at high risk of impending acute chest syndrome. High risk patients will be randomized to a simple transfusion or standard care; presence or absence of a new infiltrate on a chest radiograph done at 72 hours after randomization and/or as clinically indicated will serve as study endpoint. It is anticipated that at least 870 pain episodes will need to be screened to identify 120 subjects needed for randomization.

The Losartan study will consist of two parallel placebo-controlled trials to determine if Losartan can retard the progression of renal disease in patients with sickle cell disease (all genotypes, age  $\geq$  12 years of age). Patients with microalbuminuria (urine protein 30 – 299 mg/g creatinine) will be enrolled in one trial, while patients with macroalbuminuria (urine protein > 300 mg/g creatinine) will be enrolled in the other. Each patient will be followed for up to four years with quarterly measurements of renal function and protein excretion. It is anticipated that 4700 subjects > age 12 years of age will be need to be screened for either micro- or macroalbuminuria to identify the 450 subjects needed for enrollment and randomization.

## II. CENTER ELIGIBILITY

The SCDCRN is a collaborative group of clinical research centers which is intended to complete Phase III clinical trials. New clinical research centers will be needed to complete the clinical trials noted in Section I (Background) and may consist of a consortium of individual research sites in order to meet the eligibility criteria.

Applicants **MUST** demonstrate, by narrative and/or completion of application forms, budget justification, and tables as detailed in Section V:

1. Experience of the Principal Investigator and institution(s) in the conduct of multi-center clinical studies for non-malignant hematological disorders, particularly sickle cell disease
2. Access to a clinical research infrastructure, including
  - Institution Review Board (IRB)
  - Clinical Coordination
  - Standard Internet Access
  - Capacity to manage research medications
  - Management and staffing plan, defining the duties of each person listed
3. Access to a sickle cell disease subject population of at least 500 individuals, at least 200 of which must be adults (see Section V)
4. Commitment to clinical research conduct by proposed allocation of funds in this application for at least:
  - 0.10 FTE salary support for clinical investigators; may be for the Principal Investigator or distributed among co-investigators
  - 0.50 FTE salary support for clinical research coordination; may be for a single research nurse/coordinator or distributed among more than one individual

The SCDCRN represents a collaborative group of clinical research centers which requires frequent interactions among participants. New centers will be incorporated as full members in the SCDCRN. Applicants should explicitly express their willingness to:

- Participate in Steering Committee meetings, which occur in person 3 times a year in the metropolitan Washington DC area, and monthly teleconferences
- Abide by common definitions, common methods for patient selection and enrollment; and common procedures, tests, and reporting forms as chosen by majority vote of the Steering Committee
- Actively seek to implement each network-wide protocol approved by the Steering Committee
- Comply with study procedures and quality assurance measures approved by the Steering Committee
- Agree to oversight by the NHLBI SCDCRN Data Safety and Monitoring Board (DSMB)
- Work collaboratively with the DCC to:
  - Ensure timely computer entry and editing of study data
  - Attend/complete all required training
  - Respond to all queries promptly and clearly
  - Facilitate all site monitoring visits/audits
  - Facilitate presentation and publication of study data

---

**New England Research Institutes  
SCDCRN Data Coordinating Center**

9 Galen Street, Watertown, MA 02472 **Tel.:** 617-923-7747--- **Fax:** 617-923-4176

- Maintain adequate computer/Internet access via broadband service (daily access required)
- Report all adverse events in accordance with procedures established within the SCDCRN
- Cooperate with other members of the SCDCRN and NHLBI in the publication of study results and the eventual release to the scientific community of study procedures and other resources
- Participate in studies of the cost effectiveness of therapeutic interventions should such studies be implemented
- Accept the contract terms and conditions given below and work in a collaborative and collegial manner to foster the goals of the network
- Participate in crafting and carrying out future clinical studies
- Participate in the PROACTIVE acute chest syndrome and Losartan studies and in the selection, development, and timely completion of other SCDCRN trials

### **III. FUNDING INFORMATION**

#### **1. Mechanism of Support**

Funds will be awarded through a Subcontract with NERI funded under NIH Grant Number U10HL083721.

The Principal Investigator of each clinical research center retains the primary responsibility and dominant role for directing and executing the clinical research studies in collaboration with other members of the SCDCRN.

#### **2. Funds Available**

Approximately \$2,500,000 (direct costs) is currently available to provide core support for up to 12 additional clinical research centers over the remaining 2.25 years of the SCDCRN funding period. The proposed budget for core support of a clinical research center may not exceed \$90,000 direct costs per year. The final amount will be determined based on availability of funds. Per-patient reimbursement to be determined on a per protocol basis is also available in addition to these core funds and will be provided based on enrollment into specific protocols. Specific instructions for budget preparation are noted below. Designated funding levels are subject to change at any time prior to award, due to unforeseen budget, administrative, or scientific developments. Facilities and administrative costs are not included in the direct cost limitation.

#### **IV. CURENT FUNDING PERIOD:** January 1, 2009 through March 31, 2011

In order to correspond with NERI's grant, the budget periods (and related funding limitations) are prorated as follows:

Period 1: January 1, 2009 through March 31, 2009 (direct cost limitation \$22,500).

Period 2: April 1, 2009 through March 31, 2010 (direct cost limitation \$90,000).

Period 3: April 1, 2010 through March 31, 2011 (direct cost limitation \$90,000).

### **V. PROPOSAL SUBMISSION REQUIREMENTS**

## 1. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 11/2007). The PHS 398 application instructions are available at <http://grants.nih.gov/grants/funding/phs398/phs398.html>

a. Clinical Research Infrastructure and Experience:

Narrative description of clinical research infrastructure and experience of the Principal Investigator, co-investigator(s) and institution(s) in the conduct of multi-center clinical studies for non-malignant hematologic disorders, and commitment to participation in the SCDCRN as outlined in Section II.

b. Available Subject Population:

Provide the number of active patients, defined as patients seen at an outpatient sickle cell disease clinic in calendar year 2007 or any consecutive 12-month period starting more recently than 1/1/2007. The response, to the extent feasible, should be stratified on age and genotype, using the provided or a similar template. The number of patients receiving chronic transfusion in each stratum should also be specified. These data should be based on an adequate review and abstraction of records of potential subjects seen within the defined time period. Use the tables below as a template for providing this information.

Total patients

Genotype	Age				Total
	0-5	6-12	13-17	18+	
SS					
SC					
S $\beta^0$ -thal					
S $\beta^+$ -thal					
Other/unknown					
<b>Total</b>					

Patients on chronic transfusion

Genotype	Age				Total
	0-5	6-12	13-17	18+	
SS					
SC					
S $\beta^0$ -thal					
S $\beta^+$ -thal					
Other/unknown					
<b>Total</b>					

c. Track Record of Participation in Clinical Trials:

Provide the number of hematology multi-center studies in which patients were enrolled in the last 10 years, with the number of patients enrolled and the period of participation of the

New England Research Institutes  
SCDCRN Data Coordinating Center

9 Galen Street, Watertown, MA 02472 Tel.: 617-923-7747--- Fax: 617-923-4176

center in each study, and indicate the role of the PI and any co-investigator(s) listed on this application in each of the trials.

Complete for each trial

- 1) Study Name (indicate whether SCD Study):
- 2) Study Sponsor:
- 3) Study Type (e.g. Phase I Trial, Phase II Trial, registry, etc.):
- 4) Study period (month/yr of start & end):
- 5) Intended enrollment at site
- 6) Actual number of patients enrolled::
- 7) Role of PI and/or any coinvestigators:

d. Current Sickle Cell Disease Studies:

Provide the same information for ongoing sickle cell disease studies, including local clinical studies (not otherwise listed above), and the number of patients enrolled on each. If enrollment is open, list currently enrolled and the planned total at that site. Enrollment and target enrollment should be stratified on age (<18 vs. 18+ years).

**2. Address to Request Application Information**

Application Information may be requested at:

Dr. N.Salla Ba

Senior Research Scientist/ SCDCRN Network Manager

Sickle Cell Disease Clinical Research Network, Data Coordinating Center

New England Research Institutes, Inc.

9 Galen Street

Watertown, MA 02472

Tel: 617.923.7747 x427

FAX: 617.923.4176

email: [sba@neriscience.com](mailto:sba@neriscience.com)

**3. Budget Information:**

Applicants should complete the budget information as directed in the PHS 398 to include:

- Institutional information for the site (subcontract) institution (legal name, PI name & title, contact info and address)
- Letter/Statement of Intent signed by Institutional Official at site (subcontract)
- Face Page, signed by Institution Official
- Statement of Work/Brief Abstract
- Initial Year Budget and Entire Project Period Budget
- Budget Justification of Costs for all years
- Biosketch(s) for all **key** personnel at site
- Resources

---

New England Research Institutes  
SCDCRN Data Coordinating Center

9 Galen Street, Watertown, MA 02472 Tel.: 617-923-7747--- Fax: 617-923-4176

- NIH Checklist
- Key Personnel Form
- Other support for **key** personnel at consortium site (if applicable)
- Conflict of Interest
- Human Protection Training Certificate/Letter

#### **4. Proposal Submission Due Date:**

Applications must be received on or before **November 3, 2008**. If an application is received after that date, it will be returned to the applicant without review.

#### **5. Submission Instructions:**

Applicants must submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Dr. N.Salla Ba  
Senior Research Scientist/ SCDCRN Network Manager  
Sickle Cell Disease Clinical Research Network, Data Coordinating Center  
New England Research Institutes, Inc.  
9 Galen Street  
Watertown, MA 02472  
Tel: 617.923.7747 x427  
FAX: 617.923.4176  
email: [sba@neriscience.com](mailto:sba@neriscience.com)

## **VI. APPLICATION REVIEW PROCESS**

### **1. Review and Selection Process**

Applications will be reviewed for completeness and eligibility based on the criteria stated above by NERI. Those applications deemed incomplete or unresponsive will be returned.

### **2. Merit Review Criteria**

Applications which are complete and meet the eligibility criteria stated above will be reviewed for merit by a review committee convened by NERI, in collaboration with the SCDCRN Executive Committee, and NHLBI. This committee will include peer reviewers, selected from outside the SCDCRN and applicant pools, as well as representatives of SCDCRN, NERI, and NHLBI.

The merit of the application will be assessed with consideration of:

- Experience of the Principal Investigator, any coinvestigator(s), and institution(s) in the conduct of multi-center clinical studies for non-malignant hematologic disorders, with an emphasis on sickle cell disease
- Presence of an active clinical research infrastructure and level of commitment to sickle cell disease clinical research

- Adequate documentation of a sufficient patient pool as defined in Section V of this RFP
- Achievement and retention of targeted enrollment during previous participation in multi-center studies
- Evidence of multi-disciplinary collaboration within the participating institution(s)
- Documentation of data quality submitted in previous multi-center studies (e.g. letter of support from a Data Coordinating center or study sponsor.
- For applicants by a consortium, evidence of previous inter-institutional collaboration and a clear organizational structure.

## **VII. AWARD INFORMATION**

### **1. Award Notices**

After review of the application, the Principal Investigator will receive a written critique from the New England Research Institutes (NERI). A formal notification will be sent to all applicants regarding final status of their application

### **2. Administrative Requirements and Conditions of Award**

Awardee(s) agree to the governance of studies through a Steering Committee. Members of the Steering Committee will include the Principal Investigator from each Clinical Center (or designated alternate) and Outcome Core, the Principal Investigator from the Data Coordinating Center (or designated alternate), the NHLBI Project Scientist, and a Steering Committee chair. Meetings of the Steering Committee will ordinarily be held by telephone conference call or in the metropolitan Washington Area.

Funding will be provided through a subcontract with NERI, to be renewed annually, with an approved annual budget attached. The subcontract signed by the Vice President of Operations and Finance of NERI is the authorizing document. Selection of an application is not an authorization to begin performance.

The terms and conditions below, elaborate on these actions and responsibilities. The awardee agrees to collaborative actions with the SDCRN including the DCC (NERI) and NHLBI necessary to achieve the project objectives. It is anticipated that these terms and conditions will enhance the relationship between the NHLBI staff and the principal investigator(s), and will facilitate the successful conduct and completion of the study. These agreements will be in addition to, and not in lieu of, the relevant NIH procedures for grants administration.

The terms will be as follows:

The PI(s) in their role as members of the Steering Committee will have lead responsibilities in all aspects of the study, including any modification of study design, conduct of the study, quality control, data analysis and interpretation, preparation of publications, and collaboration with other investigators, unless otherwise provided for in these terms or by action of the Steering Committee.

1. The Principal Investigator at each clinical research center will have primary responsibility for study implementation at the center, including staff training, protocol adherence, subject recruitment and safety.

2. With the assistance of Co-Investigators as appropriate, the Principal Investigator will hire and supervise relevant personnel, obtain Institutional Review Board (IRB) approval for SCDCRN protocols, oversee data collection and adherence to study protocols and quality assurance measures, and prepare budgets and annual reports.
3. The Principal Investigator (or designated alternate) will serve as a voting member of the Steering Committee.

Awardees will retain custody of and have primary rights to their data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies. The collaborative protocol and governance policies call for the continued submission of data centrally to the coordinating center for a collaborative database; the submittal of copies of the collaborative datasets to each principal investigator upon completion of the study; procedures for data analysis, reporting and publication; and procedures to protect and ensure the privacy of medical and genetic data and records of individuals. Awardees agree to abide by the SCDCRN Presentations and Publications policy regarding dissemination of any study data and results (see Supplemental Information). The NHLBI Project Scientist, on behalf of the NHLBI, will have the same access, privileges and responsibilities regarding the collaborative data as the other members of the Steering Committee.

Support or other involvement of industry or any other third party in the study -- e.g., participation by the third party; involvement of study resources or citing the name of the study or NHLBI support; or special access to study results, data, findings or resources -- may be advantageous and appropriate. However, except for licensing of patents or copyrights, support or involvement of any third party will occur only following notification of and concurrence by NHLBI.

Study investigators are encouraged to publish and to release publicly and disseminate results and other products of studies, in accordance with study protocols and governance as well as the SCDCRN Presentation and Publication policies. Within three years of the end of the period of NHLBI support for the project, data not previously released and other study materials or products not previously distributed are to be made available to individuals who are not study investigators, provided such release is consistent with the study protocol and governance. In addition, study investigators must establish a plan for making data sets and materials available to the scientific community and to the NHLBI immediately upon completion of the three year period following the end of the period of NHLBI support.

NHLBI reserves the right to terminate or curtail the Network or any individual award or protocol thereunder in the event of (a) failure to develop or implement a mutually agreeable collaborative protocol, (b) substantial shortfall in participant recruitment, follow-up, data reporting, or quality control, (c) major breach of the protocol or substantive changes in the agreed-upon protocol with which NHLBI cannot concur, (d) attaining of a major study endpoint before schedule with persuasive statistical significance, or (e) human subject ethical issues that may dictate a premature termination. NERI reserves the right to terminate or curtail the Subcontract with the Clinical Center at the direction of NHLBI.

## **VIII. SCDCRN PUBLICATION AND PRESENTATION POLICY**

The SCDCRN undertakes unique scientific investigations affecting knowledge of the Sickle Cell patient population and its care. Because of the great effort that goes into network studies and the large amount of resources used, study investigators have the right and responsibility to communicate their findings to the scientific community and to the public at large.

The Publications and Presentations (P&P) Subcommittee is responsible for monitoring overall progress on SCDCRN publications and presentations. The P&P Subcommittee also recommends priorities for use of DCC resources for publications and presentations. These recommendations are reviewed by the Steering Committee. Generally, the highest priority will be given to papers and abstracts on the main results from SCDCRN clinical trials and other studies. Concepts for publications and abstracts should therefore be submitted to the P&P Subcommittee for review and approval before requesting access to SCDCRN data or Data Coordinating Center resources. The Protocol Chair for an SCDCRN study will serve as an ad hoc member of the P&P Subcommittee for review of any concepts for papers or abstracts on that study that are submitted by someone other than a member of the Protocol Team. It is expected that concepts submitted by members of the Protocol Team will have been reviewed by the Protocol Team, or at least the Protocol Chair, before going to P&P. To minimize the probability of inaccurate data in published materials, it is the policy of the SCDCRN that all data and text considered for all papers, and all abstracts for presentation at scientific meetings, be submitted to the P&P Subcommittee for review and approval prior to presentation or publication. The Data Coordinating Center personnel will review these materials to verify that they accurately reflect SCDCRN data.

The objectives of the SCDCRN P&P policy are:

1. To assure and expedite orderly and timely presentations to the scientific community of all pertinent data resulting from SCDCRN studies.
2. To assure scientifically accurate presentations and papers from SCDCRN investigators.
3. To assure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in the study-wide presentations and publications of SCDCRN data.
4. To assure that press releases, interviews, presentations, and publications of SCDCRN materials are accurate and objective, and do not compromise the scientific integrity of these collaborative studies.
5. To establish procedures which allow the SCDCRN Steering Committee and the NHLBI to exercise review responsibility in a timely fashion for SCDCRN publications and presentations.
6. To maintain a complete up-to-date list of SCDCRN presentations and publications, and to distribute such lists to all SCDCRN investigators and the SCDCRN DSMB on a regular basis.
7. To clarify the acknowledgment of non-NHLBI support of SCDCRN studies and publications.