Request for Letter of Intent

for

ASH Research Collaborative

Sickle Cell Disease Clinical Trials Network

DEADLINE: January 31, 2019 5:00 PM EST
ASH Research Collaborative’s Sickle Cell Disease Clinical Trials Network

Request for Letter of Intent to Participate

Overview

The ASH Research Collaborative (ASH RC) is launching a Sickle Cell Disease Clinical Trials Network ("the Network") focused on improving outcomes for individuals with sickle cell disease, by accelerating development of new therapeutics through patient engagement and optimized clinical trial execution. The Network will be a collaborative organization of clinical research sites leveraging the power of big data through the ASH Research Collaborative Data Hub ("the Data Hub") to reduce inefficiencies and increase understanding of the disease. Choosing appropriate sites able to recruit an adequate number of patients while maintaining high-quality data is crucial for an efficient and successful network. In the interest of transparency, objectivity and process standardization, the site selection is a multi-step process. First, interested institutions must submit a Letter of Intent (LOI) by January 31, 2019 to participate in the Network. The LOIs will be evaluated based on demonstration of their ability to enroll patients into trials, as well as their scientific leadership in the design and conduct of clinical trials in sickle cell disease. Second, based on the LOI, the ASH Research Collaborative will select qualified institutions and invite them to submit a full RFP, which will be issued in the Spring of 2019. Lastly, following RFP review, the selected sites will be subject to a site visit prior to admittance into the Network.

Eligible Institutions

Institutions may submit (an) application(s) if they have any of the following characteristics:

- Non-profit organizations
- For-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Eligible agencies of the Federal government
- Community-based and Faith-based Organizations

Unfortunately, institutions outside of the United States are not eligible to apply at this time.

Background

While there are currently only 2 FDA-approved drugs to treat the disease, there is a robust SCD drug development pipeline poised to drive demand for SCD clinical trials to a new level. This provides a prime opportunity to advance treatment and care of those affected by SCD:

- Currently, there are 41 products in the pipeline, and nearly 200 open studies for SCD—154 of which are recruiting patients in the United States (Sickle Cell Disease – Pipeline Insights, 2018).
- More than a dozen SCD devices are in development, and the Global SCD drug market is expected to grow by 20-45% annually through 2022 (according to the Global Sickle Cell Disease Drug Market Research Report, 2018).
- Many non-industry stakeholders are invested in addressing the burden of the disease – from policymakers to federal partners and foundations. For example, the National Heart, Lung, and Blood Institute (NHLBI) is launching a new Cure Sickle Cell Initiative – a five-year, translational research effort to provide catalytic funding to accelerate the progress and delivery of new, safe, effective gene and cell-based therapies but this initiative will not have individual clinical research sites for the conduct of clinical trials. The ASH RC CTN is well-positioned to fill a critical role by providing sites for new studies that NHLBI could fund. ASH has a Memorandum of Understanding
with NHLBI and The Cure Sickle Cell Initiative and is collaborating with NHLBI to ensure that our efforts are complementary.

- Since the FDA defines SCD as a rare (orphan) disease, SCD research and therapeutic development is eligible for numerous regulatory advantages. For example, the FDA’s Priority Review Program grants a voucher for priority review to developers of orphan drugs as an incentive to develop treatments or drugs that otherwise might not be as profitable.

The Need

There are many reasons why it is difficult to conduct clinical trials for SCD in the absence of a network. These challenges include: shortages of primary investigators, clinical trial sites, and available patients; limited access to a centralized data repository; and poor coordination among sites. An organized system to facilitate clinical trials will make the process of undertaking new studies inherently quicker, less redundant, more efficient, easier to scale, and less costly. In addition, the Network will educate patients and gather their input about the trials. The SCD patient voice has been largely absent in decisions about clinical trials in SCD, resulting in low patient support and low enrollment.

This Network will accelerate and optimize the conduct of clinical trials research in SCD by:

- Forging new relationships with patients to increase their understanding and trust in clinical trials and SCD researchers.
- Focusing on the research opportunities that hold the most promise for patients.
- Matching trial sponsors with sites.
- Facilitating the recruitment of eligible patients.
- Ensuring optimally designed trials and an efficient, coordinated approach to enrollment.
- Eliminating inefficiencies by using a centralized data repository and institutional review board (IRB).

Vision for the Network

Through patient engagement and optimized clinical trial execution, the Network will help to bring new and more effective therapies to individuals with SCD. The Network will be a collaborative organization composed of SCD clinical trials sites at academic institutions, community-based hospitals and private practices.
If the institution is in a city or state that may have multiple CTU applications, the ASH Research Collaborative strongly encourages institutions to work together and form a consortium either for the city or for the state.

Clinical Trials Units (CTUs) serve as the lead clinical trial site (applicant organization/institution) providing the scientific and administrative expertise, as well as the infrastructure to support the CTN. A CTU is an organization/institution comprised of one or more of the following components:

- At least one Clinical Research Site (CRS)
- Community Advisory Board(s)
- Laboratories
- Research Pharmacies
- Other clinical research activities (quality management, regulatory assurance and training)

The CTU must reflect a cohesive, integrated unit that has experience in relevant clinical trials. An optimal CTU configuration supports participation in multiple clinical research studies with diverse patient populations, promotes efficient use of resources and infrastructure, and successfully meets continuous performance evaluation.
The CTU must have the space (facility), dedicated staff, and the institutional commitment to ensure organizational stability and successfully accomplish the CTU’s objectives. The CTU structure must consider the location of Clinical Research Sites (CRS(s)), number of CRS(s), and involve a local Community Advisory Board (CAB). The CTU Primary Investigator (PI) is responsible for the activities and performance of the CTU. The CTU PI may also serve as the primary scientific and administrative representative(s) to the clinical research network. A qualified CTU Coordinator is responsible for overseeing the day-to-day operations of the CTU. This individual must have relevant management and clinical research experience and qualifications. The CTU Coordinator position will be funded by ASH RC up to $100,000 annually.

Clinical Research Site (CRS) is a specific location with appropriate, identified and characterized potential trial participants, where clinical trial participant recruitment, retention, protocol management, and other clinical research activities are conducted. A CRS can be a hospital, outpatient clinic, community health center, private practice, or local health department clinic. The CRS must be staffed by qualified professionals who can conduct clinical research in accordance with Good Clinical Practice (GCP), local regulatory requirements, and other applicable ASH RC requirements. CRS staff must include a CRS Leader and CRS Coordinator. The CRS Leader, an experienced staff member qualified to oversee clinical activities, will direct the activities of each CRS. The CRS Coordinator, who must also have relevant clinical research experience and qualifications, will oversee the day to day-to-day clinic operations.

The number of CRSs at an institutional location should reflect the number of personnel required to provide appropriate, cost-effective clinical research oversight for diverse populations (e.g. pediatrics, adult medicine). Where practical and efficient, applicants are encouraged to combine the operations of diverse populations into one CRS.

In addition to the CRSs listed in the application, there may be future opportunities to bring on limited protocol-specific (PS) sites to meet the needs of a specific protocol during the project period. These PS sites will be identified by the clinical research network, CTU, or ASH Research Collaborative to meet a discrete need; for example, to accomplish protocol-specific recruitment goals, if the capacity does not exist at currently funded CRSs. These PS sites will be scheduled to close upon completion of the specified protocol activities, unless the CTN requires the PS site to meet additional, identified, appropriate protocol activities. Protocol-Specific sites should not be named in this application. Protocol-specific sites will be identified and proposed after award, based on identified protocol-specific clinical research network needs.

Laboratory. Each CTU must have a network laboratory center which leads the laboratory activities that are required to carry out clinical research studies. In addition, each CRS must have access to a local laboratory capable of protocol-specific testing, as well as specimen processing, laboratory data management capabilities, shipment and storage of samples collected at the CRS. The local laboratory must be capable of communicating efficiently with the Network and sponsors. The CTUs may elect to utilize as appropriate, local laboratory services such as hospital clinical pathology departments and commercial laboratories, or provide laboratory services within the CTU. When practical and efficient, CTUs may utilize a single laboratory to support multiple CRSs. Laboratories must meet and maintain specific requirements to ensure compliance with Good Clinical Laboratory Practice (GCLP) and CLIA certification.

Pharmacy. Each CTU and CRS must have access to a secure pharmacy facility staffed by qualified pharmacist(s) in order to receive, store, manage inventory, dispense study product, and maintain accurate records in accordance with GCP, applicable United States regulations, ASH guidelines and local
requirements/regulations. The CTUs may elect to utilize appropriate pharmacy services, such as a research pharmacy operated by a medical facility, or provide pharmacy services within the CTU. When practical and efficient, CTUs may utilize a single pharmacy to support multiple CRSs. The Pharmacist(s) of Record (PoR) is/are responsible for overseeing all pharmacy-related activities.

Other Clinical Research Activities.

- **Regulatory Assurance.** Each CRS must have an efficient process to ensure compliance with all applicable regulatory requirements.
- **Quality Management.** Each CRS must also have a system for conducting internal quality control and quality assurance, consistent with ASH RC clinical research policies and standard operating procedures.
- **Staff Training.** Each CTU must have adequately trained and experienced personnel to conduct all required clinical research activities. In addition, each CTU must have a process for ongoing assessment and delivery of training to ensure staff have the appropriate knowledge and qualifications to perform required activities in accordance with GCP, ASH Research Collaborative, and Network requirements.

Community Advisory Board(s) (CABs). Each CTU must develop and implement a plan for forming and maintaining a productive partnership in the communities in which clinical research will be conducted. This partnership may be facilitated through a CAB. A CAB is an active group of individuals representing the local population(s) impacted by SCD. The organization and composition of each CAB should reflect local community representation, promote community engagement, and provide local perspective(s) on the implementation of the Network. The ASH Research Collaborative requires that each CAB should engage four distinct demographic groups within the SCD community:

- the parents of children living with SCD
- adolescents
- individuals transitioning from pediatric to adult care
- adults living with sickle cell disease and their caretakers

The CTU must determine how best to organize community partnerships to meet the research needs and priorities of the local population. This may include multiple CABs if required to enable effective representation of the populations involved, for example, to represent geographically, culturally, or other distinct populations. Two members of each CAB will represent the CTU at the ASH RC National Community Advisory Board.

Regulatory Oversight

ASH RC has selected a single IRB model. All sites participating in the Network must agree to use a single network IRB, which is Western IRB.

ASH RC Data Hub Participation

Medicine is generating an unprecedented amount of information that could transform clinical care and yield new insights into the mechanisms of disease. Recent years have seen the development and growth of professional society–driven registries designed around the needs of their specialty and their membership. While there are existing registries in SCD none are research-focused.
SCD presents unique needs, and research-focused registries offer a solution for sharing knowledge through collaboration. A single point of access for relevant information will serve as a vehicle for building a comprehensive knowledge base for SCD. Employing this valuable asset will enable researchers to more quickly and accurately answer critical questions, including disease prevalence, affected populations, and key sociodemographic data.

The significant gap in longitudinal SCD research means that there is a critical need to track patients from birth through adulthood. Furthermore, there is great potential longitudinal studies to support new SCD therapies. **Please Note: All CTN sites are required to participate in the broader ASH Research Collaborative Data Hub (ASH RC Data Hub) and share patient data with it. Additionally, participation in the Data Hub does not guarantee selection as a site in the Network. For more information on the ASH Research Collaborative Data Hub please visit the [website](#).**

**Benefits of Membership**

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<th>Type of Activity</th>
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<td><strong>Patient Engagement/Recruitment</strong></td>
<td><strong>Establish partnerships for the co-development of clinical trial educational materials for patients that include the patient voice.</strong></td>
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<td>This will benefit <strong>patients</strong> by including their perspectives on where gaps exist, what the myths are, and how to address them, filling a much-needed gap in SCD-specific clinical trial resources. <strong>Sites</strong> benefit by receiving clinical trial awareness and educational resources, as well as tools used to educate individual patients, their caregivers, and patient groups. <strong>Trial sponsors</strong> benefit from having an educated patient base that is likely more willing to participate in clinical trials.</td>
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<td><strong>Cultivate a network of SCD patient advocates to identify patients’ needs, define gaps in SCD research, and determine patient priorities for clinical trial research.</strong></td>
<td><strong>Sites and trial sponsors</strong> benefit from a clearer, more focused understanding of unmet needs, the therapeutic burden of SCD, subgroups of patients for whom therapeutics are needed, perceptions of benefit-risk, and opportunities for expanding research. This increases the likelihood patients will participate in the trials and potentially empowers <strong>patients</strong> to feel they have helped develop a meaningful treatment for their disease.</td>
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<td><strong>Increase sites’ patient recruitment performance by querying the ASH Data Hub and evaluating patients’ eligibility for a specific trial.</strong></td>
<td><strong>Trial sponsors</strong> are provided a list of sites that meet their protocol requirements and have adequate patient populations for their clinical trial. The <strong>sites</strong> benefit from receiving patient data in the ASH RC Data Hub compared against trial inclusion/exclusion criteria to yield a ranked cohort, giving site staff a targeted list of patients to engage about trial participation (patient cohort identification). This also provides potential to address <strong>patient</strong> fatigue.</td>
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**Matching Trial Sponsors to Sites**

| **Provide a site identification service to match sponsors with SCD research sites.** | **Sponsors** benefit by being matched quickly and effectively to qualified SCD sites that have the necessary resources and patient populations to conduct their clinical trial. The clinical trial landscape is competitive; the Network will |
| **Marketing** | ASH RC will embark on a marketing campaign and open dialogue with the Pharma and the Biotech Industries to bring the most compatible drug candidates for clinical trials to the Network. |
| **Staffing** | ASH RC will provide $100,000 to support a Research Coordinator for each Clinical Trials Unit (CTU). |

| **Ensuring Efficient Trials/Coordinated Approach** |  |
| **Review of study protocols.** | Provides valuable feedback to trial sponsors prior to initiation of trials, saving them time and costly protocol amendments by providing expert feedback and patient perspectives prior to protocol submission to the IRB. |
| **Feasibility assessments.** | Enables a trial sponsor to revise their protocol based on feedback from SCD experts, sites, and patients prior to the initiation of a trial. For example, if the frequency of lab tests will be a barrier for patient participation, this is flagged and recommendations for coupling the lab visit with an expected clinical visit is provided. Patients and sites benefit by less burdensome study protocols. |
| **Centralizing and sharing best SCD research practices among sites.** | These research practices will help sites to increase study efficiency and productivity. |
| **Use of a central IRB.** | Using a single central IRB for multisite clinical trials dramatically simplifies the review process. A trial sponsor has their IRB materials submitted to and reviewed by a single entity that reviews the protocol on behalf of all sites. The trial sponsor then responds to only one IRB’s feedback. This enables a study to be planned more accurately and reduces redundancies, time, and cost for trial sponsors. The resulting benefit to sites and patients is that initiation of trial can occur in a more timely and predictable manner. |
| **Specialized tools and training for clinical research staff at sites on innovative and efficient trial processes.** | This specialized training may reduce the burden of repeated training of staff at sites and improve the efficiency of clinical trials for sites and trial sponsors. |
| **Promote quality and patient safety.** | Nothing is more important than patient safety in developing new treatments for sickle cell disease. Patients are provided all the available information about the study process as well as possible risks and benefits as part of the informed consent process that is tailored to the SCD patient. Sites and trial sponsors will build a trusting relationship with the SCD patient community, empowering patients to confidently make informed decisions about their care. |
Instructions

The ASH Research Collaborative is requesting a Letter of Intent (LOI) from interested parties that are interested and qualified to join the Network.

The LOI can be no more than 5 pages, not including attachments.

- Executive Summary
- Summarize your most compelling institutional experience conducting clinical research in any disease in the last 5 years. Please provide clinical research studies which involved the SCD population. Please provide the number of subjects enrolled in each study, and the phase of study.
- Describe your prospective CTU and CRS (a typical site will consist of a Clinical Trials Unit (CTU) and the Clinical Research Site(s)—CRS(s)). Provide the rationale for the selection of the CRS(s) and which patient group that the CRS(s) provides access to. If this is a consortium, please describe its structure. Please provide an organizational chart.
- Highlight your institution’s experience in outreach and engagement with the sickle cell patient community. You can also use the experience of your prospective satellite sites. Please discuss your experience with outreach and coordination with 4 specific patient groups:
  o the parents of children living with SCD
  o adolescents
  o individuals transitioning from pediatric to adult care
  o adults
- Detail the qualifications of the personnel at the CTU and CTS(s) site by providing full CV’s as an appendix (not included in the page count). The staff includes:
  o Principal Investigator (s) at the CTU and CRS(s)
  o Coordinator (or a statement that the institution will hire one with the funds provided by ASH RC)
  o Research Pharmacist
  o Laboratory Director
- A signed letter of commitment to participate in the ASH RC Data Hub (this will not count towards the 5-page limitation for the LOI).
- The signed letter of commitment to participate with a central IRB for the Network (this will not count towards the 5-page limitation for the LOI). Please discuss your regulatory experience and any experience the institution has with single IRB that is outside of your institution. Does your institution already have SOP’s and a mechanism in place to use a single IRB that is outside of your institution? If there is an SOP and a mechanism already in place, please describe the process.
- Please discuss your institution’s experience using a contracting vehicle that consists of a Master Service Agreement (MSA) and Task Orders (TOs) for specific protocols.
  o The MSA is the primary contract that has the preamble and most of the terms and agreements, as well as a blanket Non-Disclosure Agreement (NDA). A TO is issued for each protocol accepted by the institution. The TO is a shorter contract that references the MSA and has any specific requirements for that protocol and the terms of the payments for the protocol.
• A statement of any special considerations that the CTU brings to the Network.
• Letter(s) of Support from CRS(s) on institutional letter head (this will not count towards the 5-page limitation for the LOI).
• Complete Form 1 for each CTU and CRS detailing the SCD patient population and patient demographic information (this will not count towards the 5-page limitation for the LOI). Please note that a single institution may not apply, there must be at least one CRS for the CTU application.

Formatting Instructions for LOI

Font (size, color, type density) and Line Spacing
Adherence to font size, type density, line spacing and text color requirements is necessary to ensure readability and fairness. Although font requirements apply to all attachments, they are most important and most heavily scrutinized in attachments with page limits.

The text in the accompanying attachments must follow these minimum requirements:

- **Font size:** Must be 11 points or larger. Smaller text in figures, graphs, diagrams and charts is acceptable, as long as it is legible when the page is viewed at 100%.
  - Some PDF conversion software reduces font size. It is important to confirm that the final PDF document complies with the font requirements.
- **Type density:** Must be no more than 15 characters per linear inch (including characters and spaces).
- **Line spacing:** Must be no more than six lines per vertical inch.
- **Text color:** No restriction. Though not required, black or other high-contrast text colors are recommended since they print well and are legible to the largest audience.

It is recommended that the following fonts are used, although other fonts (both serif and non-serif) are acceptable if they meet the above requirements.

- Arial
- Calibri
- Georgia
- Helvetica
- Palatino Linotype
- Times New Roman

Paper Size and Margins

- Use paper size no larger than *standard letter paper size (8 ½” x 11”).*
- Provide at least one-half inch margins (½”) - top, bottom, left, and right - for all pages. No applicant-supplied information can appear in the margins.

Orientation

- Both portrait and landscape attachments are accepted. However, keep in mind that landscape can be difficult to read online and may require reviewers and staff to scroll to see all available text.

Indication of Intent to Respond

Prospective applicants are asked to submit an indication of intent to respond that includes the following information:

- Name, address, and telephone number of the Principal Investigator
• Names of other key personnel
• Participating institutions

Although an Indication of Intent is required, it is not binding, and does not enter into the review for the subsequent application. The information that it contains allows the ASH RC Site Selection and Performance Review Subcommittee to estimate the potential review workload and plan the review. The Subcommittee consists of unconflicted reviewers. The indication of intent to apply is to be sent by the date listed at the end of this document in key dates. The indication of intent to respond should be sent electronically to:

Dr. Charles Chesson  
Director, ASH RC SCD CTN  
Email: SCD-CTN@ASHResearchCollaborative.org

Questions or Clarifications

To ensure an open and transparent site selection process, there will be a Question and Answer (Q&A) session at the ASH Annual Meeting in San Diego on December 3, 2018 at 6 pm to 7:30 pm in Room 2 at the San Diego Convention Center. The Q&A is open to all who are interested, and there is no limit as to the number of attendees per institution. RSVPs are preferred for planning purposes only. Not completing a RSVP will in no way preclude you or your institution from attending the Q&A.

Questions and responses to questions will be posted on the ASH Research Collaborative website at
www.ashresearchcollaborative.org/network.

Furthermore, questions regarding specification, requirements or the LOI process, should be directed via email to Charles Chesson, PhD at SCD-CTN@ASHResearchCollaborative.org. Answers will be provided via e-mail, and a copy of the response may be available at www.ashresearchcollaborative.org/network.

Submission of LOI

Respondents must review this Request for LOIs and reply with a formal response via email: Dr. Charles Chesson, Director, ASH SCD CTN, SCD-CTN@ASHResearchCollaborative.org. The LOI will be accepted in any of the following formats: PDF, Microsoft Word, and Microsoft Excel. LOIs must be submitted electronically no later than 5:00 PM (EST) Thursday, January 31, 2019. SCD-CTN@ASHResearchCollaborative.org. The LOI will be accepted in any of the following formats: PDF, Microsoft Word, and Microsoft Excel. LOIs must be submitted electronically no later than 5:00 PM (EST) Thursday, January 31, 2019.

It is the sole responsibility of the respondent to ensure the timely delivery of all LOI materials.

Key Dates
• Release Date: November 15, 2018
• Q&A session at the ASH Annual Meeting in San Diego: December 3, 2018 at 6 pm to 7:30 pm in Room 2 of the San Diego Convention Center
• Indication of Intent to apply Date: Monday, December 15, 2018
• Letter of Intent Deadline: Thursday, January 31, 2018
• Review by Site Selection & Performance Review Subcommittee: February 2019
• Notification Date: March 2019
Form 1 – SCD Patient Population & Demographics

Institution:

PI:

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<th>Pediatric (&lt;18 years of age)</th>
<th>Adult (&gt;18 years of age)</th>
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<td><strong>Total Number</strong></td>
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<td>Hb SS (Sickle cell anemia)</td>
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<td>Hb SC Disease</td>
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<td>Hb SB⁺ (Sickle Beta Thalassemia)</td>
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<td>Hb SB⁰ (Sickle Beta Zero Thalassemia)</td>
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<td>Other SCD disorders (Sickle D, E, or O Disease)</td>
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