Technical Assistance Webinar for "Research Network to Promote Multidisciplinary Mechanistic and Translational Studies of Sickle Cell Disease Pain" (U24, Clinical Trial Optional) (RFA-AT-24-001)

Purpose of the Webinar

On Wednesday, June 14, 2023, the National Center for Complementary and Integrative Health (NCCIH) hosted a technical assistance webinar to share information about the Research Network to Promote Multidisciplinary Mechanistic and Translational Studies of Sickle Cell Disease Pain U24 funding opportunity.

Webinar Speakers

- Inna Belfer, M.D., Ph.D., Program Director, Basic and Mechanistic Research Branch, Division of Extramural Research, NCCIH (email: inna.belfer@nih.gov)
- Marta Hamity, Ph.D., Scientific Review Officer, Office of Scientific Review, NCCIH (email: marta.hamity@nih.gov)
- Anita McRae-Williams, M.A., Outreach Communications Program Manager, Division of Extramural Research, NCCIH (webinar moderator)

Ms. McRae-Williams opened the webinar, explaining that it would be an hour long, with the first half devoted to presentations by program and review staff and the second half devoted to answering questions from the webinar participants.

Background and Rationale for the Funding Opportunity

Dr. Belfer explained that this notice of funding opportunity (NOFO) is about sickle cell disease (SCD) pain—an understudied aspect of an understudied disease. SCD is a lifelong disease that impacts an underserved minority population in the United States. About 100,000 African Americans and Hispanic Americans are affected.

Pain is the most common clinical complication of SCD. Severe acute pain episodes, chronic persistent pain, and neuropathic pain can all occur in this disease, spanning from childhood to adulthood. Even after curative therapy, severe chronic pain continues in 40 percent of individuals. Pain has a significant negative impact on the quality of life in people with SCD, leading to high rates of hospitalizations and emergency department visits, missed school or work, and poor functional and psychosocial outcomes. Pain management in SCD is complex and often doesn't address comorbidities such as anxiety, stress, sleep disturbance, and SCD complications.

In July 2021, NCCIH and the National Heart, Lung, and Blood Institute, in collaboration with other components of the National Institutes of Health (NIH), held a virtual workshop, Approaches to Effective Therapeutic Management of Pain for People with Sickle Cell Disease, to bring together experts on SCD and pain to facilitate collaborations. Workshop speakers emphasized that much is known about the genetic basis and pathophysiology of SCD, but less is known about SCD pain mechanisms. There is enormous heterogeneity in SCD pain. Patients may describe it as deep, stabbing, electrical, throbbing, beating, spreading, or "broken glass." Pain in SCD is complex. It begins with acute pain, but the type of pain may change across the lifespan. In addition to acute pain crises, most patients develop chronic pain. SCD pain, both acute and chronic, is a multi-organ clinical problem. Vaso-occlusive crises, bony

infarction, and organ damage caused by SCD can lead to acute pain in many parts of the body. Chronic pain may occur as a result of avascular necrosis or bony infarction. Musculoskeletal pain, both acute and chronic, also occurs in people with SCD.

Speakers at the NIH workshop pointed out that most clinical studies of organ damage in SCD do not measure pain and that most animal studies of SCD pain have been of limited value because they have focused on skin, which is not an organ impacted by pain in SCD patients. For example, studies of mast cell activation and sensitization of sensory nerve fibers in rodent models were done in skin. Even intervention studies, such as electroacupuncture studies, have been done in skin.

Current barriers to SCD pain research include a lack of research integration across multiple disciplines; limited connections between SCD pain researchers and other pain experts; limited opportunities for dissemination of knowledge among SCD pain researchers and between researchers, clinicians, and patients; and limited diversity and inclusion of researchers from underrepresented groups.

NCCIH has proposed creating a research network to help address these barriers. The objectives of the network will be to develop a framework to enable translational and reverse translational studies; to develop technology, such as new or enhanced animal models, pain phenotyping, imaging, and new study designs; to develop new interventions, such as nonaddictive pharmacologic therapies and complementary, integrative, or whole-person interventions; and to bring together expertise from multiple fields to study SCD pain.

Structure of the Funding Opportunity

The overall goal of this request for applications (RFA) is to promote multidisciplinary mechanistic and translational studies of SCD pain and to bring together groups of investigators from various disciplines to develop, refine, and pilot a multidisciplinary network. The four main components of the network's activities will be collaboration, pilot projects, dissemination, and clear milestones and progress evaluation.

The RFA includes both required and optional high-priority areas. The two required areas are:

- **Innovative measures and methods** to study pain in individuals affected by SCD or appropriate model systems
- **Novel mechanistic insights of pain in organ(s) impacted by SCD** in appropriate animal models or other model systems through reverse translational studies

The four optional areas are:

- **Biomarkers** predicting the transition from acute to chronic SCD pain, pain severity, and heterogeneity in different individuals, and their response to complementary and integrative health interventions
- A **whole person health approach** to SCD pain and its comorbidities
- **Multimodal interventions** for acute and/or chronic SCD pain relief
- **Therapeutic targets** for complementary and integrative health approaches

All applications must:

- Address **at least two and up to five** of the areas of interest

- Address the **potential impact** of the proposed network on mechanistic and translational SCD pain research
- Describe the type and focus areas of the **small-scale pilot projects** that will be solicited
- Provide a **formal plan** to solicit, review, select/prioritize, support, and evaluate the small-scale pilot projects
- Describe the **interdisciplinary research team** in terms of expertise and relevance to promoting multidisciplinary mechanistic and translational studies of SCD pain
- Describe **dissemination activities** to share network resources, products, and opportunities
- Articulate **clear milestones and criteria for evaluating success** of the network's efforts
- Propose specific activities for **community engagement** and population inclusion in the network's activities.

Applications that propose any of the following will be considered nonresponsive to this RFA:

- Phase I, II, or III or pivotal clinical trials.
- Traditional investigator-initiated and highly focused research projects, including pilot studies on intervention development.
- Core services to supplement the budgets of existing R01-type efforts.
- Groups of investigators at the same institution who would normally interact and collaborate in the absence of a novel initiative.
- Pilot project solicitations for clinical trials where the primary outcomes are clinical endpoints (e.g., pain or function).
- Support for scientific meetings or pre- or postdoctoral research training programs. Investigators who only seek to create research education activities should use the R25 funding mechanism.

Timeline: Letters of intent (optional but encouraged) are due September 1, 2023; **applications are due October 1, 2023;** the review meeting will be held in January 2024; and advisory council review will take place in May 2024.

Budget: Application budgets are limited to **$600,000 in direct costs per year,** and the maximum project period is **5 years.**

Review Perspective

Dr. Hamity explained that the following factors impact the review of applications:

- Responsiveness, compliance, and completeness
- The review criteria
- The review panel composition
- Key dates

Applications that are incomplete, noncompliant, or nonresponsive may not be accepted for review.

Responsiveness will be determined by program staff in collaboration with review staff. Dr. Hamity advised applicants to look for "must" and "need" when reading through the Scope and Responsiveness Criteria. To be responsive, applications must:

- Propose all the required network activities

- Address the two required and up to three optional high-priority research areas
- Span multiple disciplines
- Include a dissemination plan in the Approach section **as well as a separate data and resource sharing plan**
- Provide a formal plan to solicit, review, select/prioritize, and support small-scale pilot projects and evaluate pilot progression and outcomes in line with network priorities
- Propose novel activities that are not feasible with existing resources and funding mechanisms
- Describe milestones and criteria for assessing the value and success of the proposed activities

Compliance requirements include the following:

- The budget may not exceed $600,000 per year in direct costs.
- Applications must budget for study personnel to participate in an annual in-person meeting.
- No less than one-third and up to one-half of the proposed direct costs may be budgeted for supporting two or more pilot studies.
- The project period is up to 5 years.
- Foreign components are allowed, but foreign institutions and non-U.S. components of U.S. organizations are not.
- Page limitations are 1 page for the Specific Aims and 12 pages for the Research Strategy.
- Clinical trials are optional.
- Allowable appendix material consists primarily of blank forms. Applications submitted with appendix materials not specifically mentioned in NOT-OD-17-098 or the NOFO **will be withdrawn and not reviewed.**
- Post-submission materials are allowed (see NOT-OD-19-083). The due date is 30 calendar days before the peer review meeting date. Information accidentally left out of the application cannot be submitted as post-submission material.

Completeness requirements include the following:

- If a clinical trial is proposed, a study timeline must be included.
- Applications must comply with the instructions for Resource Sharing Plans.
- All applications must address a Data Management and Sharing (DMS) Plan.

The standard scored **review criteria** (significance, investigator[s], innovation, approach, and environment) will be used. Additional review criteria factored into the overall impact score will include the study timeline (if a clinical trial is proposed). **Language specific to this NOFO has been added to the standard five review criteria.** The aspects reviewers are asked to address match what applicants are asked to address in their applications.

Applications submitted in response to this NOFO will be reviewed in a Special Emphasis Panel at NCCIH. Reviewers will be selected based on specific areas of expertise in the target areas of the NOFO and the clinical disciplines and scientific areas proposed in the applications. Reviewers will be oriented to use the additional review criteria and additional language added to standard criteria in their assessment.

Dr. Hamity emphasized that applicants should keep in mind the need to address how their applications would be impactful considering the goals of this NOFO. She reminded applicants of the key dates already

presented, explained that the continuous submission policy does not apply to this NOFO, and explained that late applications will not be accepted.

Letters of intent should include the following information:

- Descriptive title of proposed activity
- Name, address, and telephone number of the program director(s) (PD[s])/principal investigator(s) (PI[s])
- Names of other key personnel (if known)
- Participating institutions
- Number and title of the funding opportunity

The letter should be sent to Jessica McKlveen, Ph.D., NCCIH Office of Scientific Review, at jessica.mcklveen@nih.gov.

To expedite review, NCCIH also requests that applicants notify the NCCIH Referral Office by email when their application has been submitted. Please email jessica.mcklveen@nih.gov and include the NOFO number and title, PD/PI name, and title of the application.

Dr. Hamity reviewed the following key points:

- Applications must propose all the required network activities.
- Applications must address at least two required and up to three optional high-priority research areas.
- Applications must include a dissemination plan in the Approach section as well as a separate data and resource sharing plan.
- Applications must provide a formal plan to solicit, review, select/prioritize, support, and evaluate pilot projects.
- Clinical trials are optional.
- Letters of intent are recommended but not required.
- Applications are due October 1, 2023, by 5 p.m. local time of the applicant organization.

Questions and Answers

Q1: We have developed medication monitoring technology, and SCD is a model case for the importance of taking critical medication. Our focus would be on avoiding pain through better adherence. Would this fit within the scope of this NOFO?

A1: Dr. Belfer explained that this focused scientific question may be better suited for other funding mechanisms. For the research network, NCCIH is looking for multidisciplinary collaborations and a bigger picture, rather than one specific question.

Q2: Please explain how an African American scientist could benefit from this network.

A2: Dr. Belfer said that this network aims to provide novel opportunities for investigators in the field, in particular African American investigators, in all activities the network will conduct. NCCIH hopes the network will engage all investigators, with a focus on providing additional resources to African American investigators and making their voices more prominent in the field.

Q3: Is the required dissemination plan different from the resources and sharing plan?

A3: Dr. Hamity explained that the two plans are different and both are required. The dissemination plan must be included in the Approach section. The data sharing and management plan is separate and should follow the new NIH DMS policy.

Q4: An early-career investigator with minimal publications whose practice site is at a large SCD clinic asked whether they could apply as a PI if they had a really good team.

A4: Dr. Belfer said that if this investigator had a really good team and could propose a multi-institutional, multidisciplinary collaboration, their application would be considered. However, Dr. Belfer cautioned that expertise in one area is not enough, even for an applicant with multiple publications. Collaboration and an established history of collaborations are important. A multi-PI structure would be appropriate. For example, collaborators might include an expert on SCD biology, a pain expert with experience in SCD pain or other pain conditions, someone with expertise in organ biology, and someone with experience in complementary and integrative health interventions.

Q5: It looks like this RFA is not intended to fund efficacy, effectiveness, or feasibility research except in the context of the pilot studies. What is an example of a clinical trial that could be proposed as part of the main study mechanism?

A5: Dr. Belfer said that for this RFA, clinical trials with mechanistic outcomes (such as pain thresholds or sensitivity or specific brain mechanisms underlying pain relief) are welcome, but clinical trials with clinical outcomes (such as pain intensity or pain-related function) are not.

Q6: How many grants will be funded?

A6: Dr. Belfer explained that one research network would be funded.

Q7: Does this mechanism support high-risk proposals? And must the PIs be SCD experts?

A7: Dr. Belfer said that the multidisciplinary team should include an SCD expert, but PIs with other areas of expertise can also be involved.

Q8: Will the pilot projects be conducted by the multiple PIs?

A8: Dr. Belfer explained that the network will solicit, fund, and review the pilot projects and assess their progress. The intent is that preliminary data would be collected through the pilot projects and that investigators could later submit proposals for further research using other grant mechanisms.

Q9: Who is eligible to submit an application in response to this RFA?

A9: Dr. Hamity said that any individual with the skills, knowledge, and resources to carry out the project is eligible. Applicants should keep in mind that the review criteria include specific questions regarding the applicant's expertise. She advised applicants to look at the review criteria to see whether they are a good match.

Q10: Does the one-third of the budget devoted to pilots also include the funding of a pilot core, or does it only include the money going to the pilot recipients?

A10: Dr. Belfer explained that the allocation of no less than one-third and up to one-half of the budget is for the pilots themselves. It is up to the network how to distribute these funds among the pilot projects. The criteria for the pilot projects will be established by the research network.

Q11: For dissemination to individuals with SCD, could plans include engaging with the Sickle Cell Disease Association of America and local community-based organizations at annual conferences?

A11: Dr. Belfer said this could be a good suggestion. There are many ways to approach dissemination, and community engagement is important. Dr. Belfer suggested following the recommendations in the recent report on community engagement from the National Academies of Sciences, Engineering, and Medicine.

Q12: Should this be a multiple PI application?

A12: Dr. Belfer said yes.

Q13: Can you elaborate more on the community engagement section? Are there specific outreach activities that should be addressed?

A13: Ms. McRae-Williams asked the questioner to contact Dr. Belfer after the webinar to discuss this topic.

Q14: How many awards will be funded?

A14: Dr. Belfer explained that one research network will be funded.

Q15: Is mentorship of future investigators a desired or priority activity?

A15: Dr. Belfer said that NCCIH is very supportive of training and mentorship. Activities proposed in this direction will be considered a priority.

Q16: How will administration and development of the network be shared between NCCIH and the awarded institutions.

A16: Dr. Belfer said that NCCIH will participate in some of the network activities, especially establishing core activities. NCCIH will provide programmatic support and subject matter expertise and will collaborate with the awardees. NCCIH's role will be similar to the role it has played in other U24 research networks, such as those on emotional well-being and music-based interventions.

Q17: Would small businesses that are developing treatments for SCD be qualified to apply in collaboration with doctors?

A17: Dr. Belfer said that small businesses may apply and may play different roles in the networks. They may collaborate with others as multi-PIs for the networks themselves or may be considered for pilot projects.

Q18: Can this be an international effort?

A18: Dr. Hamity explained that foreign components are allowed, but foreign institutions or a foreign component of a U.S. institution are not.

Q19: Do you plan to fund one application?

A19: Dr. Belfer said yes.

Q20: With regard to the nonresponsiveness criteria, if I submit an application with one collaborator from my institution plus one from outside my institution, would that be less competitive?

A20: Dr. Belfer explained that a goal of this network is to develop new collaborations, new projects, and new experiences not supported by other mechanisms. If you already have a collaboration with someone from your own institution, that's great for other grant mechanisms, but this funding mechanism is seeking multidisciplinary and multi-institution collaborations outside of what you would normally do.

Q21: Will this webinar be recorded, and will the recording be made available?

Q21: Ms. McRae-Williams said that all registrants will receive a comprehensive summary plus a copy of the webinar slides, which she will send by email about a week after the webinar. However, the webinar recording will not be made available.

Q22: Will you share information about who attended this webinar?

Q22: Ms. McRae-Williams explained that this information will not be shared.

Q23: Would investigations of strategies to reduce SCD pain crises be considered within the scope of this RFA?

Q23: Dr. Belfer said that the scope of the research network is to promote mechanistic and translational studies on SCD pain, in the context of complementary and integrative interventions. Research network activities must include collaboration, dissemination, milestones, and pilot projects.

Q24: If the pilot funds are suggested at $25,000 to $50,000 per pilot award, does this mean we should be trying to fund 6 to 12 pilots per year?

A24: Dr. Belfer said that the number of pilot projects is up to the network. The budget for the pilot projects can be whatever the network thinks is appropriate, within the requirement imposed by the RFA (one-third to one-half of the annual budget). The RFA does not specify the number of pilot projects.

Q25: Are indirect costs incorporated into subcontracts included in the budget limit of $600,000 per year?

A25: Dr. Hamity advised the questioner to consult with the grant management office at their own institution to discuss indirect costs.

Ms. McRae-Williams thanked the presenters and audience, and she reminded the audience that a summary of the webinar and the webinar slides will be provided in about a week. She asked participants to follow up with Dr. Belfer if they have further questions or want to discuss their specific research aims. Questions about review should be directed to Dr. Jessica McKlveen.