NIH HEAL Initiative: Coordinated Approaches to Pain Care in Health Care Systems (UG3/UH3 Clinical Trial Optional) (RFA-NS-24-041)
Technical Assistance Webinar

Purpose of the Webinar

On Thursday, September 12, 2024, the National Center for Complementary and Integrative Health (NCCIH) hosted a technical assistance webinar to share information about the notice of funding opportunity (NOFO) RFA-NS-24-041: NIH HEAL Initiative: Coordinated Approaches to Pain Care in Health Care Systems (UG3/UH3 – Clinical Trial Optional). This NOFO is supported by NCCIH and the Coordinating Center of the Helping to End Addiction Long-term Initiative®, or NIH HEAL Initiative®, Pragmatic and Implementation Studies to Improve the Management of Pain and Reduce Opioid Prescribing (PRISM) Program.

Webinar Speakers

- Anita McRae-Williams, M.A., Outreach Communications Program Manager, NCCIH (webinar moderator)
- Marlene Peters-Lawrence, M.S., B.S.N., R.N., R.R.T., Clinical Research Project Manager, National Institute of Neurological Disorders and Stroke (NINDS)
- Wendy Weber, N.D., Ph.D., M.P.H., Branch Chief, Clinical Research in Complementary and Integrative Health Branch, Division of Extramural Research, NCCIH
- Shiyong Huang, Ph.D., Scientific Review Officer, Division of Extramural Activities, NCCIH

Additional National Institutes of Health (NIH) Staff Participating

- Whitney Ratliff, Ph.D., Scientific Program Analyst, Division of Extramural Research, NCCIH

Ms. McRae-Williams welcomed the webinar participants. She explained that the webinar 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 webinar participants. All webinar registrants will receive a copy of the presentation slides and a written summary of the webinar in approximately 8 business days. Attendance at the webinar is optional and not a requirement for application submission.

NIH HEAL Initiative Overview

Dr. Weber explained that the NIH HEAL Initiative, launched in 2018 and led by Nora Volkow, M.D., director of the National Institute on Drug Abuse, and Walter Koroshetz, M.D., director of NINDS, has funded more than 1,800 research projects on pain and opioid use disorder with more than $3 billion across 50 states. Eighteen NIH Institutes and Centers have collaborated in support of this effort. She displayed a visual of what the initiative funds across four phases of research: 1) discovery, 2) preclinical development, 3) clinical trials, and 4) implementation/dissemination, noting that this UG3/UH3 funding opportunity fits into the pragmatic trials part of the implementation and dissemination area.

NOFO Overview and Background

Ms. Peters-Lawrence explained that this funding opportunity seeks to solicit applications proposing implementation science methodology to embed existing, evidence-based, coordinated pain care models into a variety of public and private health care systems where this type of care does not exist. Three to five applications for new projects are anticipated to receive funding. The application deadline is **November 7, 2024.** Late applications will not be accepted.

Ms. Peters-Lawrence explained that the National Pain Strategy report describes a need for coordinated, evidence-based pain care and highlights many barriers that hinder care delivery. Integrated pain care is an effective approach to managing pain, but hurdles to quality, coordinated pain care delivery exist. More research is needed on models of coordinated, evidence-based care delivery and on effective methods to incorporate these models into practice settings.

Key Features of NOFO Applications

Ms. Peters-Lawrence explained that applications **must:**

- Embed the coordinated care model under study into the health care delivery systems of applicant institutions
- Utilize a biopsychosocial model of pain and provide either integrated pain management centered in, and integrated with, **primary care** or provide comprehensive pain management based on referral, and in collaboration with, **primary care**
- Include multidisciplinary coordinated care approaches
- Include, at a minimum, an appropriate medication management program, psychological approaches, and physical interventions

The application can integrate pain management through referrals or collaborations with primary care providers or settings.

Ms. Peters-Lawrence displayed a visual network of a multidisciplinary approach to pain management, including aspects of primary care such as consultation, telehealth, prescription management, referrals, and rehab in the context of primary care and specialty clinics and private or nonprofit health care systems. Ultimately, the funding opportunity seeks applications integrating a multidisciplinary approach to pain management, centered in the primary care setting with appropriate specialty services.

Following submission, applications will be evaluated to see if they include a rigorous implementation clinical study embedding an effective, coordinated model of integrated pain care into the health care system. The resources and infrastructure (e.g., primary care referral system, specialty clinics, rehabilitation center, telehealth network) leveraged by the study will be considered, such as the use of existing infrastructure. To determine responsiveness, NIH will consider whether the application proposes a study centered in the primary care setting in consultation with appropriate specialty services. NIH is highly interested in applications that

involve health care systems that would benefit from coordinated pain care but do not frequently participate in research or that serve populations that are underrepresented.

Applicants are encouraged to pursue the engagement of multidisciplinary study teams in alignment with existing health care resources of the participating institution or health care system. Applicants are also encouraged to engage health care partners and stakeholders (e.g., people with lived experience, providers, health care system executives, policymakers, and payors).

Program Support

Dr. Weber explained that funded applications will be supported by the Coordinating Center of the NIH HEAL Initiative PRISM Program. She encouraged listeners to visit the Coordinating Center's website to view its many resources, tools, and textbook on how to conduct these types of studies in a health care setting. The Coordinating Center will provide technical expertise in assistance to the projects, such as input on study design, health information accessibility, and equity considerations.

The Coordinating Center will not, however, serve as a data coordinating center. Applications must have a data coordination plan and budget for these activities, such as how the study will collect data, how data will be extracted from health records, and how data will be analyzed. A biostatistician will likely be needed on the project.

All awardees will work closely with the Coordinating Center to facilitate the planning and refinement of proposed studies during the first year and to conduct the coordinated care study during the additional 4 years, with a total of up to 5 years of funding.

NOFO Definition of Coordinated Care

Dr. Weber explained that this NOFO's definition of "coordinated care" comes from the Agency for Healthcare Research and Quality (AHRQ). She noted that primary care is an essential component of either approach.

- A **comprehensive** coordinated approach provides appropriate components of coordinated pain care in a specialty clinic or rehabilitation setting in consultation with primary care.
- An **integrated** coordinated approach provides support for primary care providers to interact with related care teams to enhance evidence-based coordinated care through referral to specialty care as needed.

Other Key Features of NOFO Applications

Dr. Weber said that this NOFO is a phased award with a UG3/UH3 funding mechanism—a planning phase (UG3) and a study conduct phase (UH3). Applications must include the following:

- **A Milestone Plan Attachment.** Applications must provide proposed go/no-go transition criteria for proceeding from the planning (UG3) phase to the study conduct (UH3) phase and UH3 annual milestones to allow assessments of progress during the study conduct phase.
- **A Clinical Trial Experience Table Attachment.** Applications must display the experience of the collective team, emphasizing multidisciplinary experience, in a single table. A multidisciplinary team is required.
- **A Multidisciplinary Coordinated Pain Management Intervention.** Applications must include an appropriate medication management program, psychological approaches, physical interventions, and implementation in a primary care setting.

Be Aware of Previously Funded Projects

Dr. Weber stated that applications must be unique and nonduplicative. Applications will be deprioritized if they are similar to previously funded or ongoing trials. To learn about trials that have already been funded, visit the National Library of Medicine's PubMed database for published studies, the NIH RePORTER database for ongoing studies, and the NIH HEAL Initiative website for funded projects.

Review Considerations

Dr. Huang provided details on factors that impact the review of applications under this NOFO. He cautioned that applications that are incomplete, noncompliant, or nonresponsive to the NOFO may not be accepted for review.

Responsiveness

Dr. Huang explained that applications must be responsive to the Scope and Responsiveness Criteria in the NOFO. Responsiveness will be determined by program staff in collaboration with review staff. Look for the words "must" and "need" when reading through the NOFO, especially in the Score and Responsiveness Criteria sections. For example, the NOFO says, "The application **must** first describe the UG3 Phase and then the UH3 Phase."

For this NOFO, **nonresponsive** application criteria include:

- Applications that lack well-defined go/no go criteria with yes/no considerations to be completed in Phase 1 (UG3) to transition to Phase 2 (UH3) and well-defined milestones for each year of the proposed trial.
- Applications that fail to propose coordinated pain care that is centered in the primary care setting.
- Applications that do not include a multidisciplinary team and/or lack an implementation scientist.

- Applications that do not include multidisciplinary coordinated pain management programs that include at a minimum, an appropriate medication management program, psychological approaches, and physical interventions.
- Applications that do not propose implementation of multidisciplinary care.
- Applications that do not propose aims to assess implementation outcomes.

Compliance

Compliant applications meet the following requirements:

- **Budget**
    - The budget for the **UG3 phase** must not exceed **$625,000** per year in direct costs, while the budget for each year of the **UH3 phase** must not exceed **$1,080,000** per year in direct costs.
    - Application budgets must include a minimum effort for the program director/principal investigator (PD/PI) of **2.4 person months** to the project. If a project includes multiple PDs/PIs, the total annual PD/PI effort must be at least 2.4 person months.
- **Project Period**
    - The UG3 phase is limited to **1 year,** and the UH3 phase is limited to **4 years.** The maximum project period for both phases is **5 years.**
- **Eligibility**
    - Nondomestic (non-U.S.) entities (foreign institutions), nondomestic (non-U.S.) components of U.S. organizations, and foreign components **are not allowed.**
- **Page Limitations**
    - For this NOFO, the Research Strategy section is limited to **12 pages** (with UG3 and UH3 phases of the project combined in the total).
- **Allowable Appendix Material**
    - See RFA-NS-24-041 for a list of allowable appendix material.
- **Post-Submission Materials**
    - See RFA-NS-24-041 for allowable post-submission materials.
    - Specific to this NOFO, an **updated clinical trial experience table** and an **updated milestone plan** are allowed to be submitted as post-submission material.
    - The due date is 30 calendar days before the peer review meeting.
    - Information accidentally left out of the application cannot be submitted as post-submission material.

Completeness

To be considered complete, applications must include:

- **Clinical Trial Experience.** Applicants must provide a detailed table listing the characteristics of trials that demonstrate Key Personnel experience in trial coordination in the last 5 years. The table must be provided as an attachment called “Clinical Trial

Experience.pdf," appended with 1, 2, 3, etc., as needed, and **must not exceed three pages.**

- **Milestone Plan.** Applicants must provide an attachment called "Milestone Plan.pdf," which **must not exceed five pages.**
- **Letters of Support.** Applications must include a strong letter of support from the health care system that states their commitment to the proposed research and outlines how the project fits with organizational priorities, the quality of the proposed resources, and the commitment of their staff to the project.

Dr. Huang encouraged applicants to review Section IV of the NOFO to ensure that the application includes all requirements from the Research Strategy section.

Review Criteria

Dr. Huang discussed the review criteria for applications. **Scored Review Criteria** will include the categories of 1) Significance, 2) Investigator(s), 3) Innovation, 4) Approach, and 5) Environment (with separate scores for each). **Additional Review Criteria** will include the following areas: 1) go/no go criteria for the UG3 phase, 2) milestones for the UH3 phase, 3) study timeline, 4) protections for human subjects, 5) inclusion plans, 6) vertebrate animals, and 7) biohazards. Both scored and additional review criteria will contribute to the **Overall Impact Score.**

Aspects that reviewers are asked to evaluate will match what applicants are asked to address in the application. Additionally, NOFO-specific language has been added to the five standard review criteria. Dr. Huang advised applicants to make sure to read and take into consideration the review criteria while planning their applications.

Dr. Huang reviewed an example of matched text between submission information requested and review criteria. In the Research Strategy section (see RFA-NS-24-041 Section IV: Application and Submission Information), the NOFO states, "The application must describe details for the proposed trial including design, projections for recruitment, attrition, effect size estimations, and resources and approaches for implementation." Correspondingly, in the Approach section (see Section V: Application Review Information), the NOFO asks reviewers to consider, "How reasonable are the projections for recruitment, engagement, attrition, and effect size estimations based on the proposed HCS [health care system] settings?"

Review Panel

Applications submitted in response to this NOFO will be reviewed in a Special Emphasis Panel at NCCIH. Reviewers will be selected based on their:

- Specific area of expertise in the target areas of the NOFO
- Clinical disciplines and scientific areas proposed in the applications

Reviewers will be oriented to use the additional review criteria and the additional review language added to the standard criteria in their assessment. Dr. Huang reminded applicants to address how the application will be impactful considering the goals of the NOFO.

Important Dates

- Letters of Intent are due **October 7, 2024.**
- Applications are due **November 7, 2024 (no late applications will be accepted).**
- The review meeting will take place in **March 2025.**
- The earliest start date will be in **July 2025.**

Dr. Huang reminded listeners that the continuous submission policy **does not** apply, and late applications **will not** be accepted.

Letters of Intent

Dr. Huang noted that Letters of Intent are recommended but not required. Letters of Intent should be sent to Linda Porter, Ph.D., NINDS, at porterl@ninds.nih.gov, and must include the following:

- Descriptive title of proposed activity
- Name, address, and telephone number of the PD(s)/PI(s)
- Names of other key personnel
- Participating institutions
- Number and title of the NOFO

Questions and Answers

Q: Are there specific types of pain that this RFA is focused on (e.g., pain from musculoskeletal issues versus chronic conditions like heart disease or cancer)?

A: No, there are no specific types of pain that must be included in an application. Dr. Weber clarified that reviewers will only review applications for pain care that is managed in primary care settings. It would **not** be responsive to submit an application in which pain care is managed in an oncology clinic or a cardiovascular clinic (for example).

Q: Our team cares for pediatric cancer patients and survivors (especially adolescents). Would this be considered part of primary care?

A: It depends on the care model and whether it involves primary care. Ms. Peters-Lawrence asked whether a primary care provider is overseeing this care. Dr. Weber suggested the applicant look to the name of the facility and the associated department, noting that if it is a pediatric clinic or an internal medicine clinic, it may be considered primary care. The applicant was encouraged to reach out to Ms. Peters-Lawrence or Dr. Porter to discuss further.

Q: Can you provide some examples of target outcomes for this NOFO? Will implementation outcomes and patient-focused outcomes be equally weighted?

A: You can include both clinical and implementation outcomes; however, implementation outcomes are **required.** Dr. Weber discussed implementation outcome examples such as adoption, uptake of the intervention, and adherence to coordinated care. An implementation scientist will help to define implementation outcomes that are most relevant to the project and how to collect those outcomes in a rigorous way.

Q: Are there other instructions for multiple principal investigators (MPIs) other than 2.4 calendar months of effort?

A: If a project includes multiple PDs/PIs, the total combined annual PD/PI effort must be a minimum of 2.4 person months.

Q: Is there any chance there will be another round of deadlines if we think we need more time to pull our application together?

A: No, another round of deadlines is not anticipated. Given the complexity of this NOFO, Dr. Weber encouraged potential applicants to reach out with questions or to discuss what other funding mechanisms might be available for your research, unrelated to the NIH HEAL Initiative.

Q: The NOFO mentions having control treatment conditions. Is it acceptable to compare two approaches which have shown to be effective on a smaller scale?

A: Dr. Weber said it sounds like this would be a comparative effectiveness type of design—comparing two different implementation strategies as two coordinated care models. She believes this would be acceptable but noted that it can be difficult to interpret results if there is no "usual" condition for comparison. Dr. Weber encouraged the individual to follow up with her, Ms. Peters-Lawrence, or Dr. Porter for additional guidance.

Q: I believe the NOFO specifies that UG3 and UH3 portions of the proposal should be presented fully sequentially. Can you clarify? Is it permissible to interweave UG3 and UH3 aims and study design/methods throughout the proposal?

A: Dr. Huang noted that in Section IV of the NOFO, the "Research Strategy" section states that the application must first describe the UG3 phase and then the UH3 phase. The Research Strategy section must have a clear demarcation of the UG3 and UH3 phases of the application. Dr. Weber added that information provided in the UG3 portion does not need to be repeated in the UH3 portion of the application, as stated in the NOFO, noting that separating the UG3/UH3 portions may clarify the project for reviewers. Consider reaching out to discuss how to reference another section in your application given the challenge of the page limit. Ms. Peters-Lawrence encouraged applicants to not make the UG3 portion of the project too complex, given the 1-year time limit for the UG3 phase.

Q: Can people attending this webinar be given each other's contact information for the opportunity for a cooperation with my pain sensor technology startup?

A: No, we are not allowed to share attendee contact information with anyone.

Q: Could this program support a clinical Phase II trial on a completed Phase I drug candidate of a nonopioid analgesic oral small molecule?

A: No, this is not the appropriate funding opportunity for that type of research. Dr. Weber clarified that all the interventions proposed in these coordinated pain care models must already be evidence based and have sufficient efficacy data on them to be included. The NIH HEAL Initiative has other programs for Phase II trials. Dr. Weber encouraged the individual to check out the NIH HEAL Initiative website for more information about other funding opportunities.

Q: Are health care systems where there are pre-existing pain clinics that are largely isolated (i.e., not housed in primary care) or include only some components of the multidisciplinary pain management named in the NOFO (e.g., medication management and limited behavioral health, but no physical interventions) ruled out from pursuing this NOFO?

A: Dr. Weber encouraged the individual to reach out to a program contact to discuss their project. It sounds like there is an independent pain specialty clinic that is not housed in primary care, and this NOFO may be perfect for figuring out how the clinic can work better with primary care and not be so isolated. Ms. Peters-Lawrence said this is a good question; it sounds like more engagement needs to happen internally, but more detail is needed to answer this question.

Q: What do you call an implementation scientist? Must they have a special degree or certificate?

A: Dr. Weber said this is a really good question. Not many existing degree programs in implementation science exist or, at least, not many have existed for very long. However, there have been several certification programs and intensive trainings for implementation science; consider looking for people who have completed those types of programs or people who have completed and published large implementation trials. AcademyHealth holds an annual dissemination and implementation research conference, with agendas posted to the AcademyHealth website. This might be a resource for finding implementation scientists. Additionally, the NIH HEAL Initiative has established a Positively Uniting Researchers of Pain to Opine, Synthesize, & Engage (PURPOSE) Network, which may also provide opportunities to network and find individuals with varying expertise in the pain field and potentially implementation science expertise.

Q: There was mention of a medication management program. This implies a structured approach to medication management. Is that what the NOFO means by "medication management program"?

A: Ms. Peters-Lawrence clarified that the NOFO is asking about the institution's existing plan or structured approach to support patients through medication management. Dr. Weber added that while a medication management plan may already exist, the plan may not include certain psychological or physical elements. The NOFO seeks to help institutions develop a more coordinated, complete, and evidence-based approach to pain management and care.

Q: Are alternative therapies such as acupuncture and fascial release acceptable for this request for applications if they are in coordination with a primary care base?

A: Applications can include complementary and integrative health approaches as part of the coordinated pain care program. However, it is not required to have a complementary or integrative health care approach. Applications proposing only acupuncture or only fascial release as the intervention would not be responsive to the NOFO. Dr. Weber emphasized that the approach needs to be coordinated with all the elements described by the NOFO. For example, acupuncture can be a part of the coordinated pain care program but does not necessarily have to be provided in the primary care setting. However, the application cannot be only about acupuncture. Ms. Peters-Lawrence agreed, clarifying that if the pain care approach is a specialty area, it still requires primary care collaboration.

Q: What minimum requirements exist for the multidisciplinary team expertise, and can they all be within a primary care setting?

A: There are no limitations for multidisciplinary expertise. The types of stakeholders and care providers involved will depend on the project plan. Ms. Peters-Lawrence encouraged applicants to engage not only the primary care setting but also executive officers, providers, and individuals who live with pain conditions. Diverse engagement in the project plan will strengthen both care coordination and the project application.

Q: How does this NOFO match or dovetail with RFA-AT-24-011? Or is this NOFO totally separate?

A: Applications including veteran health care settings or U.S. Department of Veterans Affairs (VA) facilities are eligible to apply to this program. There is also a separate funding opportunity (RFA-AT-24-011) that is open right now for large-scale studies addressing pain for veterans, members of the military, and their families in VA and Department of Defense (DOD) health care settings, and Dr. Weber strongly encouraged applicants who are in a VA setting to review that funding opportunity. This NOFO is different because it allows for any health care setting that is coordinated with primary care, while the RFA-AT-24-011 opportunity requires the health care setting to be in a VA or DOD treatment facility. Another significant distinction is that this NOFO requires a coordinated pain care approach in the primary care setting, while the other NOFO does not require a primary care setting and is limited to care for veterans, members of the military, and their families. Dr. Weber invited the individual to contact her to discuss further, or to contact the RFA-AT-24-011 program contact, Peter Murray, Ph.D., at peter.murray@nih.gov.

Q: Is it preferable that the multidisciplinary team is all co-investigators, or can they be consultants and provide letters?

A: Dr. Weber said that the answer will depend on clarifying the individual's role, what they will be doing, their effort availability, and whether they will have the expertise needed to support the delivery of complex, coordinated pain care. Dr. Huang added that applicants should consider whether the expertise of the co-investigator or consultant will be sufficient from a review perspective.

Q: Will co-investigators be dinged for not having research experience since many of the collaborators will be clinicians who might not do a lot of research?

A: No, it is understood that this opportunity will engage individuals with diverse backgrounds. Dr. Weber said that the Clinical Trial Experience table will help to indicate collective team experience. Ms. Peters-Lawrence noted that this will be an opportunity to promote cross-learning.

Q: With two phases (UG3/UH3), how will my application be scored?

A: Dr. Huang said that reviewers will provide only one Overall Impact Score for both phases together, reflecting reviewers' combined enthusiasm for both phases.

Q: Will milestones influence the review score?

A: Yes. Dr. Huang explained that the go/no go criteria in the UG3 phase and the milestones in the UH3 phase are two Additional Review Criteria. Like the study timeline and the protection of human subjects, these Additional Review Criteria will be factored in along with the Scored Review Criteria to produce the Overall Impact Score. How this is balanced is dependent on the reviewers' judgment.

Q: Will the Coordinating Center provide data coordination supports such as building a database, data collection, or data cleaning?

A: No, the Coordinating Center will not assist with building a database, data collection, or data cleaning. Each application needs to include a plan and budget for these activities. The Coordinating Center can assist awarded projects with technical expertise.

Q: This funding opportunity indicates that it is "clinical trial optional." What does that mean?

A: Dr. Weber explained that most of the applications submitted in response to this NOFO will likely meet NIH's definition of a clinical trial. However, there may be some scenarios where you are doing pure implementation science, and you may not be collecting any effectiveness outcomes. In those cases, the application may not meet the definition of a clinical trial. "Clinical trial optional" enables the program to accept different types of implementation studies. Dr. Weber urged listeners to reach out for clarification or with questions about whether the proposed study meets the clinical trial definition. Program contacts can help applicants with this

and provide some examples for how to answer the questions that determine whether the application includes a clinical trial. Applicants will be required to indicate in their application whether the proposed project is a clinical trial because there is an additional set of related documents (e.g., human subjects forms) to fill out that will provide reviewers with more detail. Dr. Huang added that if your application is misclassified as a clinical trial, your application may be withdrawn. Applicants can use a clinical trial decision tool to assess whether the project meets the NIH definition of a clinical trial. If the project proposes a clinical trial, please be very careful to classify the study as a clinical trial in the application. If you are unsure, please reach out to the program official for assistance.

Q: Do investigators need to be affiliated with the health care system to apply?

A: Dr. Weber explained that you would certainly want to have somebody who is affiliated with the health care system on your multidisciplinary team, but other members of the multidisciplinary team may be affiliated with partner organizations. Multiple health care systems may be included in the application. In this case, Letters of Support from all collaborating health care systems are required. Ms. Peters-Lawrence added that this funding opportunity promotes collaboration and partnership, so reviewers will be interested to see Letters of Support as a part of the project plan.

Conclusion

Ms. McRae-Williams thanked the webinar presenters and participants, and she reminded participants that they will receive the webinar slides and summary. She encouraged participants to follow up with the program contacts listed in the NOFO. For review questions, follow up with Jessica McKlveen, Ph.D., Director of the Office of Scientific Review, NCCIH. She then closed the webinar.