## Section 1. Overview Information

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| **Participating Organization(s)** | National Institutes of Health (NIH) |
| **Components of Participating Organizations** | National Institute of Neurological Disorders and Stroke (NINDS)<br>National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)<br>National Center for Complementary & Integrative Health (NCCIH)<br>National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) Office of Research on Women's Health (ORWH)<br>National Institute on Alcohol Abuse and Alcoholism (NIAAA) National Institute of Dental and Craniofacial Research (NIDCR) |
| **Research Opportunity Title** | **HEAL Initiative: EPPIC-Net Pain Research – Protocol Application for Clinical Trial and Related Activities (OT2)** |
| **Activity Code** | OT2: Application for an Other Transaction Agreement |
| **Research Opportunity Number** | OTA-23-006 |
| **Related Notices** | OTA-19-008; OTA-20-002; OTA-20-008; OTA-22-002; OTA-23-005 |
| **Key Dates** | Posted Date: Not applicable |
| | Open Date (Earliest Submission Date): Not applicable |
| | Application Due Date(s): Rolling submission |
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## Section 2. Objectives of this Opportunity

Background: The Early Phase Pain Investigation Clinical Network (EPPIC-Net) is part of the NIH Helping to End Addiction Long-term (HEAL) Initiative designed to speed scientific solutions to stem the national opioid public health crisis. Opioid overdose deaths reached more than 80,000 annually in 2021 and more than 2 million Americans are addicted to opioids. Pain is a primary driver for the use of opioids with resultant addiction. Fifty million people, or 15% of the U.S. population, experience daily chronic pain.

The widespread use of opioids to treat acute and chronic pain contributed to the approximately 10.3 million people aged 12 years and older in the United States in 2018 who misused opioids, including heroin. These staggering numbers are likely underestimates as they fail to capture the full extent of the damage of the opioid crisis. The damage from this crisis reaches across every domain of family and community life such as lost productivity and economic opportunity, intergenerational and childhood trauma, and to extreme strain on community resources (e.g., first responders, emergency rooms, hospitals, and treatment centers). The NIH launched the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, to provide scientific solutions to the opioid crisis and offer

new hope for individuals, families, and communities affected by this devastating crisis.

There is a clear public health imperative to stimulate and support research that improves the care and outcomes of patients with severe acute and chronic pain. The Federal Pain Research Strategy (https://www.iprcc.nih.gov/federal-pain-research-strategy-overview), published in 2017, identified the development of safer non-opioid analgesics as a top priority and specifically noted the need for the discovery and validation of new pharmacologic and non-pharmacologic targets for the treatment of pain. There is also an urgent need to optimize and validate objective mechanistic biomarkers associated with pain conditions and to better understand the biologic mechanisms that underlie different pain conditions, as well as the mechanisms that tie pain conditions together. Discovery validation, development and pre-clinical testing of new targets, biomarkers and therapeutics can then be brought forward to clinical trials in humans, with, ultimately, new non-addictive treatments being brought through the regulatory approval process and into medical practice.

To address this need, the HEAL Initiative and the National Institute of Neurological Disorders and Stroke (NINDS) established EPPIC-Net. EPPIC-Net is a clinical cornerstone of the NIH's HEAL Initiative clinical program. EPPIC-Net provides a robust and readily accessible infrastructure for the rapid design and performance of high-quality early phase clinical trials to test promising novel or repurposed, non-addictive therapeutics and/or biomarkers for pain ("assets") submitted by partners in academia or industry. The trials also incorporate in-depth phenotyping and biomarker evaluation. These studies bring intense focus to patients with well-defined pain conditions and high unmet therapeutic needs.

EPPIC-Net implements novel and efficient study designs, such as adaptive and platform designs. EPPIC-Net incorporates validation studies of biomarkers and biomarker-informed proof-of-principle or target engagement studies. EPPIC-Net makes all EPPIC-Net trial data (including clinical, neuroimaging, biomarker, and preclinical data) and biosamples available through data and biospecimen repositories.

**EPPIC-Net Organization**
The EPPIC-Network infrastructure consists of one Clinical Coordinating Center (CCC), one Data Coordinating Center (DCC), and 12 Specialized Clinical Centers (SCCs) able to coordinate and conduct clinical trials across different pain conditions across the United States.

The CCC provides scientific and organizational leadership to EPPIC-Net to achieve both efficiency and excellence in the performance of clinical trials. The CCC coordinates the EPPIC-Net central IRB, establishes master contract agreements with the SCCs for trial performance, develops recruitment plans, coordinates study staff training, tracks enrollment, and oversees quality assurance and improvement. The roles and responsibilities of the CCC are described in RFA-NS-19-023.

The DCC provides scientific and organizational leadership to EPPIC-Net in all aspects of data management, data quality, statistical design, statistical analysis, and manages a publicly available biosample repository. The DCC provides data and documents for the NINDS-established EPPIC-Net Data and Safety Monitoring Board and manages reporting to regulatory authorities, including the central IRB and FDA. The role and responsibilities of the DCC are described in RFA-NS-19-024.

The SCCs provide scientific leadership and conduct the clinical trials. The SCC hubs are regional academic medical centers that both enroll patients directly and provide organizational leadership to a network of approximately 2-10 satellite "spokes" that also enroll patients. Each hub and its spokes have physicians and investigators with expertise in a wide variety of pain conditions across multiple specialties (e.g., neurology, rheumatology, obstetrics/gynecology, oncology, pediatrics, orthopedics, gastroenterology, and others), and have access to clinical populations with a broad range of pain conditions. EPPIC-Net can add ad hoc hubs/spokes if needed for specific clinical trials. The role and responsibilities of the Specialized Clinical Centers are described in RFA-NS-19-025.

EPPIC-Net utilizes a three-stage application and review process. The Stage 1 Research Opportunity Announcement (ROA; EPPIC-Net preliminary application) is open to all applicants. Applications to Stage 2 Dossier and Stage 3 Protocol are by invitation only (see Section 5: Application Information and Submission, for more information).

**Objectives**
The purpose of this ROA is to fund early phase clinical trials of pain therapeutic assets and trial-related activities. This ROA accepts applications submitted by the EPPIC-Net CCC, working in conjunction with the DCC, SCCs, and the asset applicant in developing the clinical trial.

*Applications for clinical trial preparatory activities:*
Applications for clinical trial preparatory activities must include a detailed budget and strong budget justification. Clinical trial preparatory activity applications must be for activities related to asset applications that have successfully completed Stage 2 (Dossier) review and predicated on anticipated clinical trial needs. Use of Other Transactions (OT) funding for preparatory activities will enable timely and efficient initiation of individual clinical trials as they are approved. If awarded, funding for clinical trial preparatory activities will be provided to the CCC. Preparatory activities must no overlap with those covered by EPPIC-Net U24 awards to the CCC, DCC or SCCs.

*Applications for clinical trials:*
EPPIC-Net Stage 3 applications under this ROA will only be accepted for clinical trials that were developed by the EPPIC-Net CCC after successful completion of an asset's Stage 1 (preliminary asset application) and Stage 2 (Dossier asset application) reviews.

EPPIC-Net Stage 3 applications are prepared by the EPPIC-Net CCC in collaboration with the asset Stage 1/Stage 2 applicant. The Stage 3 application will include:
- The Clinical Trial Protocol. The NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template (NOT-OD-17-064) will be used as a guideline and will be adapted to reflect the asset and population to be studied. The clinical trial protocol must include an abstract and specific aims. Submission of the Clinical Trial Protocol may be preceded by submission of a Clinical Trial Synopsis for external review and NINDS internal administrative review, however, the full protocol is required before a funding decision will be made.
- A detailed Trial Budget and Budget Justification.
- A detailed Trial Timeline and Milestones.
- A Data Management and Sharing plan in accordance with NOT-OD-21-013.

**Scope**
As well as drugs, small molecules, biologicals, and devices, EPPIC-Net can consider studies of natural products, surgical, non-pharmacological interventions, and pain-related biomarkers. EPPIC-Net studies will also incorporate investigations of biomarker discovery and validation to uncover underlying biologic mechanisms in specific pain conditions, as well as deep phenotyping and clinical characterization of its pain populations.

EPPIC-Net collaborates with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Back Pain Consortium (BACPAC) Research program. BACPAC is focused on chronic low back pain research using novel, inter- and multi-disciplinary integrated approaches, and novel analytics for discovery of disease mechanisms and features for deep patient phenotyping and identification of new targets for intervention.

## Section 3. Potential Award Information

**Please note:**
No funding is provided at EPPIC-Net application Stage 1 or Stage 2. After the EPPIC-Net 3 stage application and review process, successful asset holders obtain access to EPPIC-Net, which develops and conducts clinical trials with accepted assets in collaboration with the asset-owner. No

funding is provided to the asset holders who apply to have their therapeutics studied within EPPIC-Net. The EPPIC-Net CCC is the applicant of record for the clinical trial (Stage 3) application. If the OT clinical trial asset application is successful, the asset holder gains access to EPPIC-Net for the conduct of the clinical trial involving their asset but will not receive funding.

Stage 3 EPPIC-Net applications must not include requests for the funding of activities covered under EPPIC-Net CCC, DCC, or SCC U24 agreements, which provide funds for the EPPIC-Net infrastructure.

**Authority:**
Funding for clinical trials (Stage 3) and clinical trial preparatory activities to be executed through the EPPIC-Net program will be provided pursuant to the Other Transaction (OT) authority described in section 402(n) of the Public Health Service Act, 42 U. S. C. 282(n). Funding for newly approved EPPIC-Net Clinical Trials will usually be provided by modification of OT agreement 1 OT2 NS 122680-01.

## Section 4. Eligibility

**Organizations**
The following entities are eligible to apply under this ROA if selected after the EPPIC-Net Stage 2 review: The EPPIC-Net CCC or other entity invited by EPPIC-Net following Stage 1 and Stage 2 application review.

## Section 5. Application Information and Submission

**Application Process Overview**

*Applications for preparatory activities:*
The EPPIC-Net CCC may submit an application under this ROA for funds to initiate trial preparatory activities. These requests are not specific to a particular clinical trial and would enable timely and efficient initiation of clinical trials subsequently funded. The application must detail the ways in which the activities and/or equipment to be purchased will support anticipated clinical trials. The EPPIC- Net CCC will submit Stage 3 applications, including all required documents, via eRA Commons. Clinical trial preparatory activities applications may be reviewed by NIH program staff and will be presented to NINDS and HEAL leadership for their approval before award of OT funding.

*Applications for clinical trials*:
**Stage 1 Preliminary application (open to all eligible applicants):** The EPPIC-Net preliminary application, information, and instructions are available on the EPPIC-Net website. The brief preliminary application collects overview information on the proposed asset and associated clinical trial. Preliminary applications are submitted in eRA Commons in response to the Stage 1 ROA. The current Stage 1 ROA number must be obtained from the EPPIC-Net website at the time of submission. Stage 1 applications are received and reviewed on a rolling basis. Preliminary applications are objectively reviewed by a panel of external experts convened by NIH followed by internal NINDS administrative review. The reviews inform applications selected to move to the EPPIC-Net application Stage 2. See below for information on the review process.

**Stage 2 Dossier application (invitation only):** Based on review of the preliminary applications, asset applicants may be selected to move forward to Stage 2 of the EPPIC-Net application process. Selected applicants work with an NIH contractor to prepare a "dossier" with detailed information on the asset, including the rationale for study in EPPIC-Net, prior basic, pre-clinical and clinical research completed. Less detailed, preliminary information on the proposed study population and design will also be included. Dossiers and associated documents (e.g., cover letter, list of key personnel, Investigator Brochure) are submitted in eRA Commons under this present Stage 2 OTA ROA by the applicant. The EPPIC-Net dossier application, information, and instructions are available on the EPPIC-Net website. The Stage 2 applications are received and

reviewed on a rolling basis. The Stage 2 applications are objectively reviewed by a panel of external experts convened by NIH, including individuals who reviewed the preliminary applications along with additional experts as needed. External review is followed by internal NINDS administrative review. The reviews inform applications selected to move to the EPPIC-Net application Stage 3.

**Stage 3 Protocol application (invitation only):** Selected applicants work with the EPPIC-Net CCC and DCC and experts selected from the Clinical Sites to produce a detailed clinical trial synopsis and protocol for the asset, a budget, and a timeline. The Stage 3 application is submitted by the CCC under the present Stage 3 ROA. The Stage 3 application may include preliminary review of a protocol synopsis. However, the full written protocol will be required for review before a funding decision is made. The Stage 3 application is reviewed by the external independent/objective review panel and the NINDS administrative review committee. Protocols selected through the review process are presented to the NINDS Council and HEAL Leadership, who provide the final decision on funding award and study implementation within EPPIC-Net.

**NIH HEAL and NINDS Approval**
The final decision and approval for OT funding and to execute the protocol comes from the NIH HEAL Executive Committee and includes consideration by the HEAL Multi-disciplinary Working Group and approval of the NINDS Council. After NIH HEAL Executive Committee and NINDS Council approval, a Notice of Award will be provided, and OTA trial funds will be released to the EPPIC-Net CCC, and then the clinical trial may then begin.

**Submission Information**
EPPIC-Net Stage 3 applications are to be submitted via NIH eRA Commons. The EPPIC-Net CCC will use the current ROA when submitting the Stage 3 application in NIH eRA Commons.

**Selection Process**
*Stage 3 asset OTA applications and OT supplement applications*: NINDS selects EPPIC-Net Stage 3 (Protocol applications) based on their scientific and technical merit. Also considered are the issues identified during external expert review, internal NINDS administrative review, and relevance of the proposed project to program priorities for presentation to NINDS and HEAL leadership for approval before award of Other Transaction supplemental funding and study implementation within EPPIC-Net.

## Section 6. Independent/Objective Review Information

Assets to be studied within EPPIC-Net are selected through an independent/objective review process. There are multiple concurrent asset clinical trials.

The independent/objective review is an assessment of scientific or technical merit of applications by individuals with appropriate scientific knowledge and peer expertise. Review panel member conflicts-of-interests are appropriately managed during the review process in accordance with standard NIH policies. Independent/objective review is essential to ensuring selection of applications that best meet the needs of the program using established criteria (further outlined below) and providing assurance to the public that the evaluation and selection process is impartial and fair.

To achieve this result, NIH conducts reviews using standard practices that follow ethical standards applied to all extramural research. The review process should be viewed by practitioners, participants, and the public as credible and fair. Conflicts of interest, prejudices, biases, or predispositions will be appropriately managed during the review process.

For EPPIC-Net, reviewers provide individual assessments of the likelihood for the asset submitted to exert a sustained, powerful influence on the management of acute and chronic pain for NINDS consideration.

The Independent/objective reviewers consider only the review criteria below in their individual assessment of scientific merit. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field, or a proposed Clinical Trial may include study design, methods, and intervention that are not by themselves innovative but address important questions or unmet needs. Additionally, the results of the clinical trial may indicate that further clinical development of the intervention is warranted or that it might lead to new avenues of scientific investigation.

**Independent/Objective Review Criteria**

1. Significance
    a. Does the protocol appropriately target a specific pain condition of high, unmet therapeutic need?
    b. Is the protocol, including the scientific rationale, well-supported by current pre-clinical and clinical data, information in the literature and known biological mechanisms?
    c. Does the protocol mitigate weaknesses/critical barriers or fill gaps in prior research?
    d. Does available information and data support the need for a clinical trial for this asset and pain condition at this time?
    e. For therapeutic assets: Do the asset and proposed study represent a significant improvement over existing pain therapies for the intended target condition?
    f. For biomarkers: Do the asset and proposed study represent a significant advance in biomarker development for the condition under study?
    g. If the aims of the protocol are achieved, how will scientific knowledge or treatment development for the condition under study be advanced? If successful, will the data support the conduct of later phase clinical trials?

2. Innovation
    a. Is the asset novel or is the targeted pain condition a novel target for the asset?
    b. Is there innovation in asset utilization, such as delivery or treatment regimen?
    c. Does the protocol otherwise incorporate innovative aspects, such as in concepts, design, approaches, or methodology?
    d. Will any innovative elements enhance the study's ability to generate data that will move the field forward?

3. Approach
    a. Is the overall approach well-reasoned, feasible, and appropriate to accomplish the study specific aims?
    b. Will the approach generate balanced, unbiased data?
    c. Are potential problems identified and addressed? Are alternative strategies and benchmarks for success presented?
    d. Will the protocol provide data that will inform a subsequent go/no-go decision about whether to move the asset forward for further development and later phase clinical trials?
    e. Does the protocol identify research-related risks and provide ways to minimize those risks?
    f. Are study population selection and individual subject eligibility equitable in terms of sex, gender, race, ethnicity, age, etc? Are any exclusions justified by scientific or safety needs of the study? If applicable, will the study be able to address outcome differences due to these factors?
    g. Does the protocol adequately address the following:
        i. Study design: Does the study design enable efficient generation of clear, relevant data to address primary and secondary outcomes and inform the study hypothesis?
        ii. Is the treatment regimen (e.g., for drugs: dose, duration, route of administration; for devices: application, exposure session duration, number of sessions) and duration of the study and study phases appropriate and justified by available data?
        iii. Is the study adequately powered? Are the study cohorts well-defined,

appropriate, and informative? Are randomization, masking, and controls appropriately addressed?
   iv. Are the plans for participant recruitment, enrollment, and retention acceptable? Can the study population feasibly be obtained?
   v. Are the planned statistical approach and analyses appropriate? Is the plan for data management adequate? Can the study and data analyses be completed in a timely manner?
   vi. Are the plans for quality control, quality assurance and quality monitoring adequate?
   vii. Is the study timeline feasible?

4. Environment
   a. Will the study benefit from being conducted within the network environment?
   b. If identified, do any identified clinical sites provide an environment that can contribute to successful conduct of the study?

5. Investigator(s)
   a. If a Protocol Principal Investigator has been identified, is s/he well-suited to the study?
      i. If in an early stage of independent career development, do they have appropriate training and experience?
      ii. If established, have they demonstrated accomplishments that have advanced their fields?
   b. Do all identified investigators have leadership support and institutional governance and organizational structure appropriate for the protocol?

**Additional Review Criteria and considerations:**
As applicable for the project proposed, reviewers will evaluate the following additional criteria and considerations:

Study Timeline
1. Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well-justified?
2. Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate?
3. Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

Protections for Human Subjects
For research that involves human subjects but does not involve one of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials. For additional information on review of the Human Subjects section, please refer to the Guidelines for Reviewers: Protections for Human Subjects Review Criterion.

Inclusion of Women, Minorities, and Individuals Across the Lifespan
When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of individuals of all

ages (including children and older adults) to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research.

Biohazards
Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Select Agent Research
Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans
Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources (as applicable), are reasonable: (1) Data Sharing Plan; (2) Sharing Model Organisms; and (3) Genomic Data Sharing Plan (GDS). For additional information on data sharing, please refer to the NINDS Common Data Elements website.

Authentication of Key Biological and/or Chemical Resources
For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources. For more information, refer to NOT-OD-17-068.

Budget and Period of Support
Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

**Composition of Independent/Objective Review Panel**
Review of each stage of EPPIC-Net applications is carried out by an established panel of experts with knowledge of multiple areas of science such as pharmacokinetics, biological mechanisms, medical devices, pharmaceutical industry development, pain, and other relevant scientific and clinical expertise. A subset of the established panel is used for each independent/objective review meeting depending on the expertise needed. Additional ad hoc members are added as necessary to cover specific areas of science not included in the established panel. The review panel roster is publicly available on the EPPIC-Net website.

NIH program officials attend the review meetings to provide programmatic input. Summary statements of the review panel meetings will not be made available. However, feedback on the Independent/Objective Review and the NINDS decision on the application are provided to applicants. Appeals are not allowed.