Section 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Institute of Neurological Disorders and Stroke (NINDS)
Other Interested NIH Institutes/Centers	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) National Center for Complementary & Integrative Health (NCCIH) National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) Office of Research on Women's Health (ORWH) 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 Asset Application (OT2)**
Activity Code	OT2: Preliminary Application for EPPIC-Net
Research Opportunity Number	OTA-22-002
Related Notices	Not applicable
Key Dates:	Posted Date: 12/17/21 Open Date (Earliest Submission Date): 12/17/21 Application Due Date(s): Rolling Submission
Scientific Contacts	Barbara Karp, MD, NINDS EPPIC-Net Director barbara.karp@nih.gov.

Content by Sections

Section 2. Objectives of this Opportunity

The NIH Helping End Addiction Long-term (HEAL) Initiative seeks to speed scientific solutions to stem the national opioid public health crisis. Opioid overdose deaths reached more than 42,000 annually in 2016 and more than 2 million Americans are addicted to opioids. There are also 25 million people, or 11% of the U.S. population, who experience daily chronic pain, many of whom are prescribed opioids for pain management. New treatment options for pain are needed to reduce the number of people exposed to the risks of opioids.

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://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.

To address this need, as part of the HEAL Initiative, NINDS has established the Early Phase Pain Investigation Clinical Network (EPPIC-Net). 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 therapeutics for pain submitted by partners in academia or industry that also incorporate in-depth phenotyping and biomarker evaluation. These studies will bring intense focus to patients with well-defined pain conditions and high unmet therapeutic needs.

The purpose of this research opportunity announcement (ROA) is to invite Stage 1 preliminary applications for submission of pain therapeutics, including but not limited to, drugs, biologics, and devices as well as biomarkers (termed “assets”) for study in the HEAL Initiative’s EPPIC-Net. EPPIC-Net applications are reviewed in a three-stage process. Applications to Stages 2 & 3 are by invitation only and involve submission of more detailed information than is requested in Stage 1 (see Section 5: Application Information and Submission, for more information).

EPPIC-Net will use novel, efficient study designs including adaptive and platform designs. It will incorporate validation studies of biomarkers and biomarker-informed proof-of-principle or target engagement studies. EPPIC-Net will make all EPPIC-Net trial data (including clinical, neuroimaging, biomarker, and preclinical data) and biosamples available through public-access data and biospecimen repositories.

EPPIC-Net Organization

The EPPIC-Network infrastructure consists of one Clinical Coordinating Center, one Data Coordinating Center, and 12 Specialized Clinical Sites able to coordinate and conduct clinical trials across different pain conditions in a large number of centers across the United States.

The Clinical Coordinating Center (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 Clinical Sites for trial performance, develops recruitment plans, coordinates study staff training, tracks enrollment and oversees quality improvement. The roles and responsibilities of the CCC are described in RFA-NS-19-023.

The Data Coordinating Center (DCC) provides scientific and organizational leadership to EPPIC-Net in all aspects of data management, data quality, statistical design, statistical analysis, and through managing a biosample repository. The DCC supports the Data and Safety Monitoring Board and manages reporting to regulatory authorities (e.g., central IRB, FDA). The role and responsibilities of the DCC are described in RFA-NS-19-024.

The Specialized Clinical Centers provide scientific leadership and conduct the clinical studies. The Specialized Clinical Centers (hubs) are regional academic medical centers that both enroll patients directly and provide organizational leadership to its network of 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 has the ability to add ad hoc hubs/spokes if needed, for particular clinical trials. The role and responsibilities of the Hubs are described in RFA-NS-19-025.

Scope

EPPIC-Net is specifically seeking pain therapeutic assets that are phase 2-ready. Assets that are FDA-regulated should have an existing FDA IND/IDE or sufficient documentation to submit an IND/IDE application to the FDA.

EPPIC-Net is open to assets targeted to any pain condition and population, adult or pediatric. As well as drugs, biologicals, and devices, EPPIC-Net may consider studies of natural products, surgical, and non-pharmacological interventions. EPPIC-Net will also incorporate investigations of biomarker discovery and validation within clinical studies of proposed pain therapeutics to uncover underlying biologic mechanisms in specific pain conditions with deep phenotyping and clinical characterization.

Assets with known addiction potential will be deemed non-responsive and will not be considered. Assets with a mechanism of action known to be associated with addiction potential and lacking preclinical data on addiction potential or likeability will be deemed non-responsive and will not be considered. Assets focused solely on a potential opioid sparing indication will be deemed non-responsive and will not be considered. Concerns about whether an asset is within EPPIC-Net's scope can be discussed with program staff prior to submitting an application.

The proposed asset must have completed first-in-human studies and have preliminary information on safety in humans and sufficient data to inform dose selection for a phase 2

clinical trial. Potential applicants are STRONGLY encouraged to contact EPPIC-Net Program Staff to discuss the application and application process prior to submission. Applications deemed non-responsive to terms of this ROA will not be considered for EPPIC-Net.

EPPIC-Net is collaborating with the NIH Back Pain Consortium (BACPAC) Research program administered by NIAMS. The BACPAC Research Program is focused on chronic low back pain employing, multidisciplinary, integrated approaches to address the mechanisms of chronic low back pain and response to treatment, through deep patient phenotyping, the identification of new targets for intervention and the development of new technologies. More information can be found in the following notices: NOT-AR-19-022 (https://grants.nih.gov/grants/guide/notice-files/NOT-AR-19-022.html), NOT-AR-19-023 (https://grants.nih.gov/grants/guide/notice-files/NOT-AR-19-023.html), NOT- AR-19-024 (https://grants.nih.gov/grants/guide/notice-files/NOT-AR-19-024.html), and NOT-AR-19-025 (https://grants.nih.gov/grants/guide/notice-files/NOT-AR-19-025.html).

For purposes of this ROA, NCCIH is interested in applications proposing clinical trials of devices or natural products (e.g. botanicals, dietary supplements, or probiotics) relevant to complementary health interventions for the treatment of any pain condition.

Section 3. Potential Award Information

Please note:
No funding is provided to the asset holders for study of their therapeutic within EPPIC-Net. After the EPPIC-Net 3 stage application and review process (described below), successful asset holders gain access to EPPIC-Net, which develops and conducts clinical trials with accepted assets in cooperation with the asset-owner. NIH Other Transaction funds to conduct the study are awarded to the EPPIC-Net CCC, which administers the funds to other EPPIC-Net research components.

Authority:
This Research Opportunity Announcement (ROA) is issued with the goal of soliciting novel pain therapeutic "assets" to be studied within EPPIC-Net. Assets are selected through a multi-stage application and review process. An application that is successful at all three stages will result in the asset being eligible for study in EPPIC-Net and in the award of other transactions (OT) funds provided to the EPPIC-Net CCC to administer for conduct of the study pursuant to 42 U.S.C. § 282(n).

Section 4. Eligibility

Organizations
The following entities are eligible to apply under this ROA:

Higher Education Institutions
- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs) Tribally Controlled Colleges and Universities (TCCUs) Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments

- State Governments County Governments
- City or Township Governments Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized) Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession Independent School Districts

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)

Faith-based or Community-based Organizations

- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

- Non-domestic (non-U.S.) Entities (Foreign Institutions) are eligible to apply
- Non-domestic (non-U.S.) components of U.S. Organizations are eligible to apply.
- Foreign components, as defined in the NIH Grants Policy Statement (https://grants.nih.gov/grants/policy/nihgps/HTML5/section_16/16.2_eligibility.htm?Highlight=Foreign%20Component%27), are allowed.

Eligible Individuals (Program Director/Principal Investigator): Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an asset application. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Section 5. Application Information and Submission

Application Process Overview

Academic, industry and other investigators may submit an application to have their therapeutic candidate "asset" (e.g., novel drug, biologic, and devices) studied within EPPIC-Net.

There are 3 stages of application and review:

Stage 1 Preliminary application: The EPPIC-Net preliminary application packet is available at: https://www.ninds.nih.gov/Current-Research/Trans-Agency- Activities/NINDS-Role-HEAL-Initiative/NINDS-Role-HEAL-Initiative-EPPIC. The preliminary application requests summary/overview information on the proposed asset and associated clinical trial. Preliminary applications are submitted in response to this Stage 1 Research Opportunity Announcement (ROA). Stage 1 applications are received and reviewed on a rolling basis. The review includes the independent/objective review by a panel of external experts convened by NINDS. Applications also undergo an internal NINDS administrative review to evaluate for responsiveness and for the fit of applications to the EPPIC-Net program. See below for information on the independent/objective review process"

Stage 2 Dossier application: Asset applicants with highly rated preliminary applications are selected to work with an NINDS contractor to prepare a "dossier" with detailed information on the asset, including prior basic, pre-clinical and clinical research completed and rationale as well as brief information on the proposed study population and design. Dossiers are submitted by invitation only under a separate Stage 2 OTA ROA. Stage 2 applications are also received and reviewed on a rolling basis with intermediate pre-determined review cut-off dates. Stage 2 applications are likewise objectively reviewed by a panel of external experts convened by NINDS, including individuals who reviewed the preliminary application along with additional experts as needed.

Stage 3 Protocol application: Asset applicants with highly rated dossiers are selected to work with the EPPIC-Net to develop the asset-specific clinical protocol. Specifically, within 90 days of dossier approval, the EPPIC-Net CCC and DCC, together with the applicant and experts selected from the Specialized Clinical Centers, produce a detailed clinical trial protocol for the asset, a budget, and a timeline for submission under the Stage 3 OTA ROA. If appropriate, the application could include a proposal for additional clinical sites from outside the network. The final protocol, budget, and timeline comprise the Stage 3 (OTA) application to be submitted by the CCC, which is then reviewed by the external independent/objective review panel convened by NINDS, including potential additional experts if required. Highly rated protocols are presented to the NINDS Council and HEAL Leadership for consideration for OT funding.

NIH HEAL and NINDS Approval

The final decision and approval for an Other Transaction (OT) Award and to execute the protocol comes from the NIH HEAL Executive Committee and

includes consideration by the HEAL Multi-disciplinary Working Group and of the NINDS Council. A Notice of Award will be provided.

After NIH HEALExecutive Committee approval, OT trial funds are released to EPPIC-Net CCC and the clinical trial may begin.

Important Reminder: There is no funding associated with this research opportunity announcement. This ROA is solely for the first stage of a 3-stage application process. NIH Other Transaction funds to conduct the study are awarded to the EPPIC-Net CCC for conduct of the trial *only after successful completion of all 3 stages of application and review, and approval by the NIH HEAL Executive Committee.*

Submission Information
Applications to EPPIC-Net are submitted via NIH eRA Commons. https://public.era.nih.gov/commons/public/login.do?TARGET=https%3A%2F%2Fpublic.era.nih.gov%2Fcommons%2FcommonsInit.do . Use this ROA number when submitting the preliminary application in NIH eRA Commons.

Upon receipt, applications are evaluated for completeness, compliance with application requirements and responsiveness by NINDS. Applications that are incomplete, non-compliant and/or nonresponsive will not be reviewed and the applicant will be so notified.

Section 6. Independent/Objective Review Information

Assets to be studied within EPPIC-Net are selected through an independent/objective review process. It is anticipated that there will be multiple concurrent 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. The 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 was 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.

Reviewers individually provide an assessment of the likelihood for the asset under review to exert a sustained, powerful influence on the management of acute and chronic pain, or transition from acute to chronic pain.

Independent/Objective Review Criteria:
Significance

- Do the asset and approach appropriately target a specific type of pain with high unmet therapeutic need?
- Do the asset and approach represent a marked improvement over existing pain therapies?
- Will the asset and proposed study notably advance the field of pain therapy?

Viability/Feasibility

- Is the asset appropriate for the proposed indication? Would another indication be a better fit for the asset?
- Have preliminary studies (e.g. for safety) been completed so that the asset is IND/IDE ready?
- Does the information provided indicate readiness for a Phase 2 Clinical Trial?
- If the clinical trial is successful, is there a path forward for eventual clinical adoption?
- Are there barriers to use of the asset in the proposed study or eventually for clinical use?
- Is the asset reasonably safe for study in a phase 2 clinical trial in the formulation/design and dose proposed?

Scalability/Readiness

- Is the proposed strategy for testing this asset in a Phase 2 Clinical Trial suitable? If not, could a suitable trial strategy be developed, with the understanding that the EPPIC-Net CCC will ultimately provide the final clinical trial design?
- Is sufficient asset available for a Phase 2 Clinical Trial. If not, are well-defined plans in place for producing an adequate supply of the asset for trial in a timely manner?
- Will the asset be scalable for eventual clinical use?
- Is there a reasonably rapid timeline for bringing this asset to a clinical trial?

Composition of Independent/Objective Review Panel

From an established panel of expert reviewers, a sub-set is assembled for each independent/objective review depending on the expertise needed for the specific applications to be reviewed. Additional ad hoc members are added as necessary to cover specific areas of science not included in the main panel. The review of the EPPIC-Net preliminary applications is carried out by experts with knowledge of multiple areas of science such as pharmacokinetics, biological mechanisms, medical devices, pharmaceutical industry development, pain, and relevant scientific and clinical expertise.

The review panel roster is posted on the EPPIC-NET website. NIH program officials attend the reviews to provide programmatic input. There are no consensus scores or summary statements from the panel reviews. However, feedback from the independent/objective review, NINDS administrative review and the decision on the application are provided to applicants. Appeals are not allowed.