

Section 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Institute of Neurological Disorders and Stroke (NINDS) 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 – Dossier (OT1)
Activity Code	OT1: Pre-Application dossier for an Other Transaction Award
Research Opportunity Number	OTA-20-002
Related Notices	OTA-19-008
Key Dates:	Posted Date: Not applicable
	Open Date (Earliest Submission Date): Not applicable
	Application Due Date(s):
	Rolling Submission; close date for this submission round will be on the EPPIC-Net webpage
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Section 2. Objectives of this Opportunity

Background: EPPIC-Net is part of the NIH Helping 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 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 \(https://iprcc.nih.gov/Federal-Pain-Research-Strategy/Overview\)](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, the HEAL Initiative and NINDS have established the Early Phase Pain Investigation Clinical Network (EPPIC-Net). EPPIC-Net is a cornerstone of the NIH's Helping to End Addiction Long-term (HEAL) Initiative. 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.

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-Net 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 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 has the ability to add ad hoc hubs/spokes if needed for particular clinical trials. The role and responsibilities of the

Specialized Clinical Centers are described in [RFA-NS-19-025](#)

Objectives

The purpose of this research opportunity announcement (ROA) is to invite Stage 2 Dossier applications for submission of assets that have successfully passed Stage 1 preliminary application review. EPPIC-Net applications are reviewed in a three-stage process. Applications to Stages 2 & 3 will be by invitation only (see Section 5: Application Information and Submission, for more information).

Applicants who are invited to submit a Stage 2 application will work with an NINDS-designated contractor to prepare their dossier application. The dossier application will incorporate detailed information on

- the proposed therapeutic, including the proposed target, mechanism of action, drug pharmacokinetic and pharmacodynamic profile and/or device specifications.
- the target, context of use, type of sample needed (for biomarkers).
- the proposed intervention rationale and procedures (for behavioral studies).
- data from any existing IND, IDE or Investigator Brochure.
- pre-clinical data on mechanism of action, target engagement, and safety, including addiction potential.
- the proposed pain indication and population (assuring diversity) and how the therapeutic asset will address the unmet pain need

Scope

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 and clinical studies to uncover underlying biologic mechanisms in specific pain conditions with deep phenotyping and clinical characterization.

EPPIC-Net is collaborating with the NIAMS Back Pain Consortium (BACPAC) Research program. BACPAC is focused on chronic low back pain research using novel, inter and multidisciplinary integrated approaches and novel analytics for discovery of disease mechanisms and features for deep patient phenotyping and identification of new targets for intervention. 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>).

Section 3. Potential Award Information

Please note:

No funding is provided to the asset holders who apply to have their therapeutics studied within EPPIC-Net. After the EPPIC-Net 3 stage application and review process (described below), successful asset holders obtain access to EPPIC-Net, which will develop and conduct 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 and biomarkers to be studied within EPPIC-Net and to enable invited Stage 1

applicants to submit a Stage 2 dossier application. Assets will be selected for study in a clinical trial in EPPIC-net through a multi-stage application and review process. Successful application will result the asset being eligible for study and in the establishment an “other transactions award (OTA)” agreement with funds provided to EPPIC-Net Centers and Sites for conduct of the study pursuant to 42 U.S.C. § 289g-5.

Section 4. Eligibility

Organizations

The following entities are eligible to apply under this ROA if selected after the EPPIC-Net Stage 1 review:

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 applications requests summary/overview information on the proposed asset and associated clinical trial. Preliminary applications will be submitted in response to the Stage 1 Research Opportunity Announcement (ROA), [OTA-19-008](#). The Stage 1 applications will be received and reviewed on a rolling basis with intermediate pre-determined review cut-off dates. These preliminary applications will be objectively reviewed by a panel of external experts convened by NIH. See below for information on the review process.

Stage 2 Dossier application: Asset applicants with high ranking preliminary applications will be selected to work with an NIH contractor to prepare a “dossier” with detailed information on the asset, including prior basic, pre-clinical and clinical research completed as well as information on the study population, design, and rationale. Dossiers will be submitted under this present Stage 2 OT1 ROA. The Stage 2 applications will be received and reviewed on a rolling basis with intermediate pre-determined review cut-off dates. The Stage 2 applications will be objectively reviewed by a panel of external experts convened by NIH, including individuals who reviewed the preliminary applications along with additional experts as needed.

Stage 3 Protocol application: Asset applicants with top-ranking dossiers will be selected to proceed to work with the EPPIC-Net to develop the study-specific clinical protocols. Specifically, within 90 days of dossier approval, the EPPIC-Net CCC and DCC, together with the applicant and experts selected from the Clinical Sites, will produce a detailed clinical trial protocol for the asset, a budget, and a timeline that will then be submitted under the Stage 3 OT2 ROA. If appropriate, the application could include a proposal for additional clinical sites from outside the network. The final protocol, budget, and timeline will make up the Stage 3 (OT2) application which will then be reviewed by an external objective review panel, including potential additional experts if required. Meritorious protocols will be presented to the NINDS Council and HEAL Leadership, who will approve meritorious protocols for funding and study implementation within EPPIC-Net.

NIH HEAL and NINDS Approval

The final decision and approval for an Other Transaction Award (OTA) and to execute the protocol will come from the NIH HEAL Executive Committee and will include consideration by the HEAL Multi-disciplinary Working Group and approval of the NINDS Council. A Notice of Award will be provided.

After NIH HEAL Executive Committee and NINDS Council approval, OTA trial funds will be released to EPPIC-Net CCC and the clinical trial may begin.

Important Reminder: there is no funding associated with this specific research opportunity announcement. 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.*

Submission Information

Dossier 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%2Fcommonslnit.do> . Use this ROA number when submitting the application in NIH eRA Commons.

Section 6. Objective Review Information

Assets to be studied within EPPIC-Net will be selected through an objective review process. It is anticipated that there will be multiple concurrent asset clinical trials.

Objective review is an assessment of scientific or technical merit of applications by individuals with appropriate scientific knowledge and peer expertise. 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 will conduct 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 will individually provide an assessment of the likelihood for the asset submitted to exert a sustained, powerful influence on the management of acute and chronic pain.

Objective Review Criteria:

1. Significance
 - a. Do the asset and approach appropriately target a specific type of pain with high unmet therapeutic need?
 - b. Do the asset and approach represent a significant improvement over existing pain therapies?
 - c. Will the asset and proposed study significantly advance the field of pain therapy?
 - d. If the asset overlaps (in terms of mechanism of action, target or approach) with existing pain therapeutics, is there innovation in delivery or some other aspect?
 - e. Does the asset have a proposed target (if known) with a strong rationale and rigorous supporting data to justify testing in the specific pain condition proposed?
2. Feasibility
 - a. Is the asset appropriate for a Phase 2 Clinical Trial within EPPIC-Net?
 - b. Does the overall conceptual framework for moving this asset to a Phase 2 Clinical Trial remain realistic?
 - c. Are there any barriers to moving the asset into Phase 2 Clinical Trial studies?
 - d. Is the proposed path for clinical adoption realistic?
 - e. If prior development of the asset was stopped, does that barrier remain a concern?
 - f. Is the asset clearly scalable for both the proposed clinical trial and eventual clinical use?
 - g. Are safety and biohazard considerations for use of the asset in humans clearly addressed?
 - h. Is there a reasonably rapid timeline for bringing this asset to a clinical trial?

3. Data

- a. How robust are the pre-clinical data in support of the proposed asset provided?
- b. How robust are the clinical data in support of the proposed asset provided?
- c. For drugs:
 - i. How robust is the pharmacokinetic/pharmacodynamic information?
 - ii. How are the scale-up, good manufacturing practices, and needed resources addressed?
- d. For devices:
 - i. How sound are the mode of use and supporting data?
 - ii. How are device manufacturing, controls, and safety standards addressed?
- e. For Drugs and Devices
 - i. Is manufacturing consistent with relevant standards and safety testing (ISO, IEC, IEEE, etc.)?
 - ii. Does the regulatory history show that the asset is IND/IDE ready?
 - iii. How is the competitive landscape addressed?
 - iv. Are the estimated costs justified?
- f. For biomarkers:
 - i. Is the rationale reasonable?
 - ii. How is the biomarker an improvement over existing biomarkers and safety/efficacy endpoints?
- g. Is the Target Product Profile (TPP) adequately addressed?

4. Approach

- a. Are novel methods, assays, or approaches proposed?
- b. With the understanding that the trial design will be fully developed for the final, Stage 3, application review, is the preliminary design proposed in the dossier appropriate for stated goals of trial and the indication?

Composition of Objective Review Panel

Review of the EPPIC-Net preliminary applications will be carried out by an established panel of experts with knowledge of multiple areas of science such as pharmacokinetics, biological mechanisms, pharmaceutical industry development, pain, and other relevant scientific and clinical expertise. A subset of the established panel will be used for each objective review meeting depending on the expertise needed. Additional ad hoc members will be added as necessary to cover specific areas of science not included in the established panel. The review panel roster will be made publicly available on the EPPIC-Net website once several review meetings have been completed.

NIH program officials will attend the review meetings to provide programmatic input. Summary statements of the review panel meetings will not be made available. However, feedback on the Review Outcome will be provided to applicants. Appeals will not be allowed.

Review panel member conflicts-of-interest will be guided by current NIH policy and practices.