

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) 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 (OT2) |
| Activity Code | OT2: Pre-Applicationdossier for an Other Transaction Award |
| Research Opportunity Number | OTA-23-005 |
| Related Notices | OTA-19-008; OTA-20-002; OTA-20-008; OTA-22-002, OTA-23-006 |
| 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) (<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 research opportunity announcement (ROA) is to invite submission of Stage 2 Dossier applications for assets that have successfully passed Stage 1 preliminary application review.

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

- For drug and device assets: the proposed therapeutic, including its purported target, mechanism of action, drug pharmacokinetic and pharmacodynamic profile and/or device specifications.
- For biomarkers assets: the target, context of use, and type of procedure or sample needed for biomarkers.
- Data from any existing Investigational New Drug (IND), Investigational Device Exemption (IDE), or Investigator Brochure.
- Existing pre-clinical and clinical data on asset mechanism of action, target engagement, safety, addiction potential, and potential efficacy.
- The proposed pain indication and population for the asset, indicating how the therapeutic asset will address the unmet pain need.

The dossier application submission can include a cover letter that addresses any concerns raised during the asset's preliminary application review. The dossier application should include a list of the key personnel, including consultants, delineating their roles in the proposed study as well as anyone with a potential conflict of interest.

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 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 develops and conducts clinical trials with accepted assets in collaboration with the asset-owner. NIH Other Transaction (OT) funds to conduct the study are awarded to the EPPIC-Net CCC, which administers the funds to the SCCs and other EPPIC-Net research components.

Authority:

This 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 are selected for study in a clinical trial in EPPIC-Net through a multi-stage application and review process. A successful Stage 3 application renders the asset eligible for study and for funds under an “Other Transactions” agreement provided to the CCC to administer to EPPIC-Net Centers and Sites for conduct of the asset clinical trial pursuant to the authority described in section 402(n) of the Public Health Service Act, 42 U. S. C. 282(n).

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](#), are allowed.

Eligible Individuals (Program Director/Principal Investigator): Any individuals with the skills, knowledge, and resources necessary to carry out the proposed research as the Program

Directors/Principal Investigators (PDs/PIs) are 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” (i.e., drug, biologic or device) studied within EPPIC-Net.

There are 3 stages of EPPIC-Net application and review:

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 independently and objectively reviewed by a panel of external experts convened by NIH followed by internal NINDS administrative review. The independent/objective reviews inform applications selected to move to the EPPIC-Net application Stage 2. See below for information on the independent/objective review process.

Stage 2 Dossier application (invitation only): Based on independent/objective 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 independently and 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, after which the clinical trial may then begin.

Submission Information

Dossier Applications to EPPIC-Net are submitted via NIH eRA Commons. Use the current ROA number when submitting the dossier application in NIH eRA Commons.

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. 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 therapy?
- 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?
- i. Does the proposed asset have a feasible pathway to eventual commercialization?

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 modes 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 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 independent/objective review panel meetings to provide programmatic input. Summary statements of the review panel meetings are not provided to applicants. Applicants will be notified of review outcome and key review issues by NINDS EPPIC-Net program staff. Appeals will not be allowed.