Section 1. Overview Information

<table>
<thead>
<tr>
<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
</tr>
</thead>
</table>
| 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 – Clinical Trial Protocol (OT2) |
| Activity Code | OT2: Application for an Other Transaction Agreement |
| Research Opportunity Number | OTA-19-011 |
| Related Notices | OTA-19-008; OTA-20-002 |
| Key Dates: | Posted Date: Not applicable |
| | Open Date (Earliest Submission Date): Not applicable |
| | Application Due Date(s): Rolling Submission; the close date for each submission round will be posted on the EPPIC-Net webpage |
| Scientific Contacts | Barbara Karp, MD, Program Director EPPIC-Net, NINDS  
[barbara.karp@nih.gov](mailto:barbara.karp@nih.gov) |
| | Rebecca Hommer, MD Program Official EPPIC-Net, NINDS  
[rebecca.hommer@nih.gov](mailto:rebecca.hommer@nih.gov) |

Content by Sections

<table>
<thead>
<tr>
<th>Overview Information</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives of this opportunity</td>
<td>2</td>
</tr>
<tr>
<td>Potential Award Information</td>
<td>3</td>
</tr>
<tr>
<td>Eligibility</td>
<td>4</td>
</tr>
<tr>
<td>Application Information and Submission</td>
<td>5</td>
</tr>
<tr>
<td>Independent Review Information</td>
<td>6</td>
</tr>
</tbody>
</table>

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), 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 its trial data (such as clinical research data, neuroimaging, and biomarker 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 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

EPPIC-Net applications are reviewed in a three-stage process (https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative/NINDS-Role-HEAL-Initiative-EPPIC). Stage 1 (EPPIC-Net preliminary application; ROA OTA-19-008) is open to all applicants. Applications to Stages 2: (ROA #OTA-20-002 & 3 (the present ROA) 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 EPPIC-Net applicants who have been accepted after Stage 1 (preliminary application) and Stage 2 (dossier application) to work with the EPPIC-Net Clinical Coordinating Center (CCC) on application stage 3: Application for OT Agreement.

The EPPIC-Net Stage 3 application will be prepared by the Clinical Coordinating Center (CCC) in collaboration with the original asset 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 for the protocol. That template will be adapted to reflect the asset and population to be studied.
- Detailed Trial Budget
- Detailed Trial Timeline and Milestones

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


**Section 3. Potential Award Information**

**Please note:**
No funding is provided at EPPIC-Net application Stage 1 or Stage 2. Funding will be awarded for successful Stage 3 applications.

The Stage 3 EPPIC-Net application will be submitted by the EPPIC-Net Clinical Coordinating Center. If the Stage 3 application is successful, the Stage 1/2 asset applicant does not receive funding but will gain access to EPPIC-Net for the conduct of the clinical trial involving their asset.

It is anticipated that there will be multiple concurrent asset clinical trials.

**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 assets selected after dossier review (Stage 2) applications to move to Stage 3 of the EPPIC-Net application and
review process- Clinical Trial Protocol development, application and review. Stage 3 applications selected following a robust independent process, will be accepted for study in EPPIC-Net. NIH/NINDS/EPPIC-Net and the EPPIC-Net CCC will enter into an Other Transaction Agreement for the conduct of the study. OT Agreements are used to fund clinical trials to be executed through the EPPIC-Net program, pursuant to OT 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 2 review:

Eligible Individuals (Program Director/Principal Investigator): Any individual(s) identified by EPPIC-Net CCC (located at Massachusetts General Hospital) as having the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s). PD(s)/PI(s) identified by the CCC will work with the asset owner to develop a Clinical Trial Protocol. 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

There are 3 stages of application and review:

Stage 1 Preliminary application: Academic, industry and other investigators may submit a preliminary application to have their therapeutic candidate “asset” (e.g. pain therapeutic drug, biologic, or device or pain biomarker) studied within EPPIC-Net. The Stage 1 Research Opportunity Announcement (ROA #OTA-19-008) and the EPPIC-Net preliminary application packet are available at: https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative/NINDS-Role-HEAL-Initiative-EPPIC

Stage 2 Dossier application: Following independent review, selected Stage 1 applicants are invited to apply to stage 2, Dossier application. The Stage 2 Research Opportunity Announcement (ROA), (ROA #OTA-20-002) and application information can be found at: https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative/NINDS-Role-HEAL-Initiative-EPPIC

Stage 3 Protocol application: Following independent review, selected Stage 2 applicants are invited to proceed to Stage 3, Protocol application. At stage 3, the asset holder will work with the EPPIC-Net CCC, Data Coordinating Center (DCC) and experts within EPPIC-Net to develop the Stage 3 application per the “Objectives” section above. The EPPIC-Net CCC will be the applicant for Stage 3 and will submit the Stage 3 application, including all required documents, via eRA Commons. The Stage 3 application will undergo independent review. Protocols selected following review will be presented to the NINDS and HEAL Leadership for their approval before award of Other Transaction funding and study implementation within EPPIC-Net.

Submission Information
Section 6. Independent, Objective Review Information
Assets to be studied within EPPIC-Net undergo objective, independent review.

Independent review is an assessment of scientific or technical merit of applications by individuals with appropriate scientific knowledge and expertise. Conflicts-of-interests of review panel members are appropriately managed during the review process in accordance with standard NIH policies. Independent review provides information essential to ensuring selection of applications that best meet the needs of the program using the criteria delineated below and that application selection is conducted in a fair, objective manner free of prejudices and biases.

Reviewers provide individual assessments of the likelihood for the asset submitted to exert a sustained, powerful influence on the management of pain for NINDS consideration.

The Independent 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 unwarranted 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?
   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? Are 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?
   ii. Is the study adequately powered? Are the study cohorts well-defined, appropriate and informative? Are randomization, masking, and controls appropriately addressed?
   iii. Are the plans for participant recruitment, enrollment, and retention acceptable? Can the study population feasibly be obtained?
   iv. 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?
   v. Are the plans for quality control, quality assurance and quality monitoring adequate?
h. Is the study timeline feasible?

4. Environment
   a. Will the study benefit from being conducted within the network environment?
   b. 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

a. 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?

b. 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?

c. 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).
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.

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 complementary knowledge of multiple areas related to the proposed study subject matter and the conduct of clinical trials 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 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 is posted 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.

Selection Process

NINDS will select EPPIC-Net Stage 3/Protocol applications based on their scientific and technical merit, including consideration of the issues identified during independent/objective review and relevance of the proposed project to program priorities for presentation to NINDS and HEAL Leadership for their approval before award of Other Transaction funding and study implementation within EPPIC-Net.