

## Section 1. Overview Information

<b>Participating Organization(s)</b>	National Institutes of Health (NIH)
<b>Components of Participating Organizations</b>	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)
<b>Research Opportunity Title</b>	<b>HEAL Initiative: EPPIC-Net Pain Research - Application for Clinical Trial and Related Activities (OT2)</b>
<b>Activity Code</b>	OT2: Application for an Other Transaction Agreement
<b>Research Opportunity Number</b>	OTA-20-008
<b>Related Notices</b>	OTA-19-008; OTA-20-002
<b>Key Dates:</b>	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
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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 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 (SCCs) 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](#)) and Stage 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 fund early phase clinical trials of pain therapeutic assets and its related activities. The ROA accepts applications from the EPPIC-Net CCC, working in conjunction with the EPPIC-Net DCC and SCCs, for funding of clinical trial preparatory activities not covered by EPPIC-Net U24 agreements to the CCC, DCC, or Specialized Clinical Centers (Hubs/Spokes), as well as applications for specific clinical trials.

#### *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 review and predicated on anticipated clinical trial needs. Use of Other Transaction (OT) funding for preparatory activities will enable timely and efficient initiation of individual clinical trials as they are approved.

#### *Applications for clinical trials:*

Applications for adding clinical trial under this parent OTA opportunity will be accepted only for those 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. Applications for clinical trials will undergo independent Stage 3 EPPIC-Net review. Clinical trial proposals not submitted in the original application for the parent OT Agreement will be submitted as supplements to the original application.

The Stage 3 clinical trial supplements (not part of the original application) will be prepared and submitted by the EPPIC-Net CCC in collaboration with the original 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 for the protocol. That template will be adapted to reflect the asset and population to be studied.
- Detailed Trial Budget and Budget Justification
- 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.

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 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. More information can be found in the following notices: [NOT-AR-19-022](#), [NOT-AR-19-023](#), [NOT-AR-19-024](#), [NOT-AR-](#)

[19-025](#), and [NOT-AR-20-016](#).

## 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 clinical trial preparation applications and clinical trial supplement applications.

The EPPIC-Net CCC is the applicant of record for the clinical trial (Stage 3) asset application or supplement. If the OT clinical trial asset application is successful, the asset holder will gain access to EPPIC-Net for the conduct of the clinical trial involving their asset but does not receive OT funds.

Neither OT clinical trial parent applications nor OT clinical trial supplement applications may 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.

It is anticipated that there will be multiple concurrent asset clinical trials funded through OT clinical trial parent application and supplements.

### **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 by enabling assets selected after dossier review (Stage 2) applications to move to Stage 3 of the EPPIC-Net asset application and review process (Clinical Trial Protocol development, application and review) and to enable clinical trial preparatory activities. The OT Agreement will be used to fund clinical trials (Stage 3) and clinical trial preparatory activities 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**

#### *Applications for Parent OTA application:*

Following receipt and independent review of Stage 3 applications, clinical trial preparatory activities and/or equipment may be identified by NIH program staff that relate to anticipated clinical trials but are not specific to a particular clinical trial and which would enable timely and efficient initiation of clinical trials subsequently funded. The EPPIC-Net Clinical Coordinating Center may submit a “parent” OTA application requesting funding for these limited, non-study-specific activities

and equipment and detailing the ways in which they will support anticipated clinical trials. These preparatory activities and equipment may not include those already funded under the EPPIC-Net CCC, DCC, or SCC U24 agreements, which provide for the EPPIC-Net infrastructure. The EPPIC-Net CCC will submit the parent OTA application, including all required documents, via eRA Commons. These applications will be limited to clinical trial-related activities and purchases identified through and common to reviewed clinical trial supplement Stage 3 applications (see below), and clinical trial proposals that have already undergone independent objective review (also known as “Stage 3” review, see below). The parent OTA application will undergo administrative review by NINDS staff and will be presented to NINDS and HEAL leadership for their approval before award of Other Transaction funding.

*Applications for clinical trial supplements (not part of the parent application):*

There are three stages for EPPIC-Net asset application and review. The 3<sup>rd</sup> stage constitutes an application for clinical trial supplements under this ROA.

**Stage 1 Preliminary asset 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 asset 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 asset (Clinical Trial Supplement) application:** Following independent review, selected Stage 2 applicants are invited to proceed to Stage 3, Protocol asset 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 the Stage 3 and will submit the Stage 3 application, including all required documents. Once the parent OTA is in place, additional Stage 3 applications will be submitted as a supplement to the parent OTA application via eRA Commons. The Stage 3 clinical trial supplement 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

*Applications for clinical trial preparatory activities (Parent OTA applications) and applications for clinical trial supplements (Stage 3 asset applications) will be 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. Independent, Objective Review Information

### Review of Stage 3 clinical trial preparatory activities applications (Parent OTA

## **applications):**

Applications for clinical trial preparatory activities will undergo administrative review by NINDS staff. The review will take include consideration of the objective, independent review of relevant clinical trial supplement/Stage 3 asset applications.

### **Review Criteria**

- 1) Fit with EPPIC-Net mission
  - a. Do the proposed activities and purchases advance the EPPIC-Net mission of novel, efficient pain clinical trials?
  - b. Do the proposed activities and purchases advance the EPPIC-Net mission to incorporate biomarker validation and biomarker-informed proof-of-principle or target engagement studies?
  - c. Do the proposed activities and purchases advance the EPPIC-Net mission to make its trial data and biosamples available through public-access data and biospecimen repositories?
- 2) Justified need and relevance to anticipated trials
  - a. Do the proposed activities and purchases support anticipated non-study specific needs related to clinical trial supplement/Stage 3 asset applications that were favorably reviewed to date?
  - b. Do the proposed activities and purchases support aspects deemed relevant and critical, rather than ancillary, to clinical trial supplement/Stage 3 asset applications that were favorably reviewed to date?
  - c. Will the proposed activities and purchases enable timely and efficient initiation of clinical trials under review for OTA funding?
- 3) Absence of overlap with activities covered under standing EPPIC-Net U24 Cooperative Agreement awards

### **Review of Stage 3 asset applications (supplements):**

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



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**

*Applications for clinical trial preparatory activities (Parent OTA application):* Applications for clinical trial preparatory activities (parent OTA applications) will be selected through the administrative review according to the criteria described above and will be presented to NINDS and HEAL Leadership for approval before an Other Transaction award is made. Clinical trial protocols included in the parent OTA application will follow independent objective review procedures described for Stage 3 asset applications above.

*Stage 3 asset applications (supplements):* 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 approval before award of Other Transaction supplemental funding and study implementation within EPPIC-Net.