Early Phase Pain Investigation Clinical Network (EPPIC-Net)
Application and Review Webinar

March 26, 2021
Webinar Agenda

1:30-1:40 HEAL Initiative: Overview and Update
   • Rebecca Baker, PhD, Director, NIH HEAL Initiative

1:40-1:50 EPPIC-Net: Network Overview and Application Process
   • Barbara I. Karp, MD, Program Director, EPPIC-Net

1:50-2:00 EPPIC-Net Review Process
   • Ana Olariu PhD; Shanta Rajaram, PhD; NINDS Scientific Review Officers

2:00-2:10 EPPIC-Net Application via eRA Commons
   • Laurie Roman, PhD, eRA Commons

2:10-2:30 Moderated Q and A
Crisis #1: National Overdose Deaths

- Drug overdose deaths have increased dramatically in 15 years
- After a period of leveling, new increases in 2019 and 2020
- COVID-19 has had a profound impact on the ongoing opioid epidemic
  - Increased rates of drug use and overdose
  - Challenges to treatment, patients and communities

National Public Health Emergency declared in 2017
Crisis #2: Chronic Pain in the U.S.

- 50 million adults are affected by chronic pain
- 25 million report severe pain on a daily basis
- 20 million have high impact chronic pain

CDC, Morbidity and Mortality Weekly Report, Sept. 2018
The Response:
$500 million/year Sustained Research Investment

25+ HEAL Research Programs

- Prevention – Basic & Translational Research – Clinical Trials – Implementation Science

- 12 NIH ICs leading studies
- Trans-NIH governance structure
- Partnerships across government, communities, and the private sector
NIH HEAL INITIATIVE RESEARCH OVERVIEW

ENHANCING PAIN MANAGEMENT

IMPROVING TREATMENTS FOR OPIOID MISUSE AND ADDICTION

- Novel Medications Options
- Translating Research Into Practice
- Enhanced Outcomes For Affected Newborns
- New Prevention & Treatment Strategies
Clinical Research in Pain Management

• Early Phase Preclinical Investigation Network (EPPIC Net)
  o 14 grants for infrastructure; NINDS led
  o Trial under development for CCR2 antagonist for knee osteoarthritis pain

• Back Pain Consortium
  o 14 research projects; NIAMS led
  o 3 mechanistic research centers, 7 technology sites, 2 phase II trials, data center, and 1 supplement to study back pain in the context of OUD

• Hemodialysis Opioid Prescription Effort (HOPE)
  o 8 clinical sites, data center; NIDDK led
  o Test non-pharmacological interventions and buprenorphine for pain in patients in kidney dialysis
Clinical Research in Pain Management

• **Pain Effectiveness Research Network (ERN):**
  o 8 projects; NCATS infrastructure with NICHD, NIA, NIAMS, NIDA, NINR, NCI trials
  o Pain conditions studied: knee osteoarthritis, postsurgical pain in adolescents, post-mastectomy pain, acute pain post cesarean, chronic pain in cancer survivors, chronic pain in veterans with OUD

• **Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing (PRISM):**
  o 7 projects; NCCIH NIA, NIAMS, NINR
  o Nonpharmacological management of diffuse fibromyalgia pain, post-surgery, sickle cell and chronic low back pain
Clinical Research in Pain Management Accomplishments

- Data harmonization through a set of pain-unique Common Data Elements for HEAL clinical pain studies
- Iterative model to inform precision medicine for chronic low back pain
  - Multiple contributions to chronic low back pain and treatment interventions — from anxiety to tissue damage and from psychotherapy to surgery
- FDA IND for use of buprenorphine for pain management as part of multidisciplinary pain management for patients on dialysis for end stage renal disease
Cross-cutting HEAL themes

• Sharing and open access of data
  o HEAL Public Access and Data Sharing Policy
  o Secure infrastructure for making HEAL data FAIR
  o Harmonized measures established by HEAL teams

• Engagement of research participants, patients, and stakeholders

• Importance of partnerships, diversity and inclusion in HEAL research studies
HEAL Data Ecosystem

- Enable access of HEAL data for various stakeholders through a user-friendly web portal
- Foster secondary research and new discoveries
- Maximize access to and use of data analysis tools and resources
- Provide sustainability of HEAL digital assets beyond individual awarded programs

“We are committed to making data from this investment rapidly available for use by policymakers, patients, and clinicians and importantly, to other scientists within and outside of HEAL to promote new discovery”
Use Cases: Engagement with the HEAL Data Platform

As a community-based service organization, we want to support people misusing opioids in our communities in order to save lives and reduce suffering.

As a clinician treating patients with chronic pain, I want access to the latest pain research and clinical trial results to identify and track potential new approaches to assist my patients.

As a research expert in opioid misuse and addiction, I want to compare different psychosocial interventions to optimize medication-based treatment approaches for opioid use disorder.

As a pain translational researcher, I want to validate a pain drug target in multiple species in order to have a complete evaluation of a possible novel pain drug target.
NIH • Helping to End Addiction Long-term

www.heal.nih.gov
Early Phase Pain Investigation Clinical Network (EPPIC-Net)

About the Program

March 26, 2021
Barbara Illowsky Karp, MD

NIH HEAL Initiative and Helping to End Addiction Long term are service marks of the U.S. Department of Health and Human Services.
EPPIC-Net Goal

Reduce reliance on opioids by accelerating early-phase clinical trials of non-addictive pain therapeutics ("assets"), including drugs, small molecules, biologics and devices (NOT-NS-19-043)

EPPIC-Net provides

- Phase 2 clinical trials for accepted assets from Industry and Academia. Assets can be novel or re-purposed. Must be phase 2 ready (with IND/IDE or IND/IDE ready)
- Proposal should focus on specific pain population/condition with high unmet need
- Proof-of-concept testing/validation of biomarkers
- Well-characterized adult and pediatric pain patient cohorts
- Incorporation of deep phenotyping into trials
- Innovative study design
- Continuous learning from experience to engineer adaptive, ever-improving early-phase testing of new pain therapies
EPPIC-Net Infrastructure

NIH/HEAL/NINDS: interacts with all EPPIC-Net components, provides guidance/oversight of budget and milestones

Asset Provider: provides the pain therapeutic (drugs/device etc.) for study; *retains IP/property rights to asset*

Clinical Coordinating Center: (MGH) develops protocol in collaboration with asset provider, matches hubs/spokes to protocol/asset, oversees trial conduct, distributes and manages trial funds.

DCC: (NYU) receives and centralizes data, provides statistical input and analyses, harmonizes data, provides reports to regulatory agencies, manages EPPIC-Net biorepository

Clinical Hubs/Spokes: (see EPPIC-Net website for listing) identify trial investigators, recruit and enroll participants, conduct the trial study procedures, collect and report data to DCC and CCC
**Stage 1: Preliminary application**
- Applicant completes and submits brief preliminary application in eRA Commons (1-2h)
- Independent objective and NINDS admin reviews

**Stage 2: Dossier application**
- Selected applicants work with NINDS contractor to prepare dossier. Applicant submits in eRA Commons
- Independent objective and NINDS admin reviews
- Selected dossiers work with CCC to develop protocol/budget. Submitted by CCC in eRA Commons

**Stage 3: Protocol application**
- NINDS Council Review
- Independent objective and NINDS admin reviews
- Trial OT agreement signed. Trial set-up begins

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NIH HEAL INITIATIVE

EPPIC Net Application Webinar 3/26/21
The preliminary application packet is available on the EPPIC-Net and HEAL websites

1. EPPIC-Net and application overview
2. EPPIC-Net preliminary application (fillable pdf)
3. Line-by-line instructions for preliminary application
4. eRA Commons Instructions

POTENTIAL APPLICANTS ARE STRONGLY ENCOURAGED TO TALK TO US BEFORE SUBMITTING AN APPLICATION

The preliminary application asks only for high level information

- Asset identification, class, mechanism of action
- Brief citation of pre-clinical and clinical studies supporting asset
- Known safety concerns
- Proposed indication, dose/exposure, route of administration
- What makes asset unique/better than others in class or for indication
- Freedom-to-operate letter from asset owner

Common reasons for prelim application failure to move forward

- Asset not phase-2 ready
- No clear advantage over available therapeutics in same class
- Weak scientific basis
- Safety concerns
### Application process: dossier application

Selected applications work with an NINDS contractor to prepare the Stage 2/Dossier application.

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<tr>
<th>Dossier sections</th>
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<tr>
<td>Summary</td>
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<tr>
<td>Scientific Rationale and Unmet need</td>
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<tr>
<td>Asset Biology, Pharmacology, and/or Physiology</td>
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<tr>
<td>Target Product Profile</td>
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<tr>
<td>Non-clinical Data (pharmacokinetics, safety pharmacology)</td>
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<tr>
<td>Toxicology Summary</td>
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<tr>
<td>Prior Clinical Experience</td>
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<td>Asset Preparation for clinical trial</td>
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<tr>
<td>Competitive Analysis</td>
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<tr>
<td>Additional Considerations (e.g. need for EPPIC-Net in asset development)</td>
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### Applicant role in dossier development

- Provide contractor with detailed information to support dossier.
- Provide FDA filings, IB
- Address prelim application reviewer concerns in dossier
- Submit dossier in eRA Commons

### Contractor protects confidentiality

Timeline: 3 working weeks
Application process: Protocol Application

Selected applicants work collaboratively with the EPPIC-Net CCC (and DCC) to prepare the trial protocol & budget

- A Protocol Principal Investigator with appropriate expertise for asset/condition is chosen from EPPIC-Net investigators
- Study population finalized
- Trial design may be novel; may incorporate placebo and active controls
- May incorporate biomarker evaluation/validation
- Role of applicant in trial defined
- Budget and timeline developed
“Other Transaction” Awards are used to fund EPPIC-Net Clinical Trials
*OT award is made to CCC for distribution for trial conduct. The asset owner does not receive funds.

Successful applicants receive access to EPPIC-Net for the development and completion of the asset clinical trial. Data from the clinical trial can be used to support further therapeutic development and later phase trials.

The Asset Holder/Applicant is expected to provide the therapeutic asset for the clinical trial. The Asset owner retains intellectual property rights.

EPPIC-Net is open U.S. and non-U.S. applicants
EN20-01: A 24-week Week Study to Evaluate the Safety and Efficacy of CNTX-6970 in Subjects with Moderate to Severe Knee Osteoarthritis Pain

Study Design: Randomized, allocation concealed, multicenter, placebo-controlled, multi-crossover: 150 patients; randomized 1:1:1

Randomized treatment allocation

- CNTX 100mg bid/placebo
- CNTX 300mg bid/placebo
- Celecoxib 100mg bid/placebo

Randomized order allocation

Each allocation group is randomized further into two 12-week blocks with different drug/placebo order
EPPIC-Net Staff Contacts

EppicNet@ninds.nih.gov

• Barbara I. Karp- karpb@ninds.nih.gov
• Rebecca Hommer- rebecca.hommer@nih.gov
• Jennifer Beierlein- jennifer.beierlein@nih.gov
• Marlene Peters-Lawrence – marlene.peterslawrence@nih.gov
Independent/Objective Review

Independent/Objective Reviews are NOT standard NIH Peer Reviews!!
## EPPIC-Net Review process

<table>
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<tr>
<th>Stage</th>
<th>WHAT:</th>
<th>WHO:</th>
<th>AWARD:</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>Preliminary Application (brief asset data)</td>
<td>Asset applicant</td>
<td>NO</td>
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<tr>
<td>Stage 2</td>
<td>Dossier Application (in depth asset data)</td>
<td>Asset applicant working with NINDS Contractor</td>
<td>NO</td>
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<tr>
<td>Stage 3</td>
<td>Clinical Trial Protocol</td>
<td>EPPIC-Net CCC (with DCC, Hub PIs and Applicant)</td>
<td>YES</td>
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### Independent/Objective Review Panel
Evaluates assets based on template, full dossier, and clinical protocol

- **NIH IC Staff**
- **HEAL MDWG**
- **NINDS Council**
- **NIH HEAL Executive Committee**
EPPIC-NET Application Submission and Review Process

Applicant/Asset

Stage 1
Preliminary application → Objective application review #1

Stage 2
Dossier application (invitation only) → Objective application review #2

Stage 3
Objective application review #3

NINDS Council & HEAL Review

Clinical Coordinating Center

Data Coordinating Center

EPPIC-NET Centers

Research Hubs/Spokes

NIH HEAL INITIATIVE
Goals of Independent/Objective Review

• To have a fast, fair streamlined review process.
• To get input from the outside experts for NINDS/HEAL consideration of EPPIC-NET awards.
• Obtain reviewers’ *individual opinions* on each proposed therapeutic
  o Consensus is NOT the goal.
• Conflicts of Interest (COI) will be managed using principles of NIH review COI policy, as a guide.
Independent/Objective Review Panel

• 20-30 Core panel members. Same Panel reviews EPPIC-NET applications at each application stage, although not all members are present at every meeting.

• Expert *ad hoc* reviewers with special expertise are added at each stage as needed to cover science, rigor, and methodology.
Application submission and Independent/Objective Review process

- Preliminary applications (Stage 1) are submitted on a rolling basis.
  - Meeting cut-off dates are posted on the EPPIC-NET webpage

- Dossier (Stage 2) and Clinical Protocol (Stage 3) applications are submitted by invitation only and are submitted in eRA Commons under different ROA numbers.

- EPPIC-Net reviews are conducted on a rolling basis determined by the number and timing of application submissions.
Stages 1, 2 and 3: Independent/Objective Review

Different review criteria matched to stage of review.

- **Stage 1 (preliminary application)** – High level evaluation. Focus on the asset suitability for EPPIC-NET with consideration of target population. Less emphasis on proposed trial design.

- **Stages 2 (dossier application)** – Emphasis on drug/biologic asset pharmacology or asset device specifications and pre-clinical/clinical data in support of the asset for the proposed population. Early consideration of proposed clinical trial design.

- **Stage 3 (protocol application)** – Thorough review of all aspects of the clinical trial. Review also includes consideration of criteria such as Protection of Human Subjects, safety monitoring, and Inclusion plans (gender, minorities, and individuals across life span).
Application Review Outcome

• Pre-meeting individual reviewer’s assessment will identify key strengths and weaknesses and an initial recommendation for a color “Bin”.

  GREEN – Meritorious

  YELLOW – Meritorious but some concerns noted

  RED – Not deemed meritorious, serious concerns noted; may NOT be discussed
Post-Objective Review process/Funding decisions

• Post-Independent/Objective review, the NINDS convenes an internal administrative review committee consisting of NINDS program officers knowledgeable about pain and clinical trials.

• NINDS EPPIC-NET staff will notify the applicants of selection decisions and decision-driving concerns. Review Summary Statements are NOT provided to applicants.

• The final decision for funding a *Clinical Protocol application (Stage 3)* lies with the NINDS Director with NINDS Council considerations and HEAL leadership.
EPPIC-Net: Preparation, Submission & Tracking in eRA Commons

Laura M. Roman, MBA, PhD
eRA Commons

- Submitting organization must be registered at eRA Commons
- Streamlined Commons registration process: no DUNS required for submission
- Organization much have an individual with role of Signing Official
- PD/PI must have Commons ID and be affiliated with submitting organization
Application Preparation & Submission in ASSIST

• ASSIST is NIH’s System to System solution
• Application preparation, submission & tracking in a single system
• Streamlined submission- single form + attachments
• Use opportunity provided in EPPIC-Net (OTA-21-005) in this format
• If PI completes profile in eRA commons, can use Commons ID to prepopulate select fields in the application
Users can access ASSIST through eRA Commons or directly using [https://public.era.nih.gov/assist](https://public.era.nih.gov/assist) or searching for NIH ASSIST from your browser.
Unique identifier for application: 21115
Complete information for organization, PI and business officials
Fields with * are required

Save and keep locked prevents someone else from working on the form at the same time. Save and release lock, returns form to status where it can be edited by someone else.
Only individuals with signing official role can submit.
The system will validate the application.
Errors must be corrected.
Clicking accession number (in red circle) will take the user to eRA Commons to view assembled application image.
• Bookmarks and TOC
• Separate attachment fields identified by file names
• Communications to applicants regarding status
Q&A

Please submit your questions in the Q&A box
Thank You!

This webinar will be posted on the EPPIC-Net Program page.

Please contact EPPICNet@ninds.nih.gov with further questions.