NIH/NINDS Opportunities for Pain and Migraine Research

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Program Director, Pain & Migraine
National Institute of Neurological Disorders and Stroke
co-Chair HEAL Preclinical and Translational Pain Research
<table>
<thead>
<tr>
<th>Clinical Trial Readiness</th>
<th>Phase I</th>
<th>Phase Ib</th>
<th>Phase Ila</th>
<th>Phase IIb</th>
<th>Phase III</th>
<th>Phase IV</th>
<th>Dissemination Implementation CER</th>
</tr>
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<tbody>
<tr>
<td>First in Human</td>
<td>First in target population</td>
<td>Proof of Concept (Biomarker)</td>
<td>Preliminary Efficacy (Clinical)</td>
<td>Definite Efficacy</td>
<td>Post Marketing Surveillance</td>
<td>PAR CT Readiness</td>
<td></td>
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**PAR Exploratory Clinical Research**

**Cooperative Programs in Clinical Research PAR Phase II/III CTs**

- SIREN
- NeuroNEXT
- StrokeNet
- HEAL EPPIC-NET

**Biomarker Discovery/Validation**

**Outcome Discovery/Validation**

**Clinical Trial Embedded Natural History Studies**

**Common Data Elements**
NINDS Clinical Trial Networks

- **EPPIC-NETT**: Coming 2019
- **NEuroNEXT**: Phase II/biomarkers 2011-present
- **HEAL**: Exploratory Trial Phase II Coming 2019
- **NIH StrokeNet**: 2013-present
- **NIH SIREN**: Emergency Trials Network 2017-present
- **Acute Care**: 2006-2018

Processes:
- Exploratory Trial
- Phase II/III Trial
- Adaptive design
- Phase III Trial
Overview

- Network will include HUBs with Migraine/Headache Expertise
- **Phase II studies**
- **Infrastructure applications in Feb 2019**
- A cornerstone of the NIH’s Helping to End Addiction Long-term (HEAL) Partnership
- Provides a robust and readily accessible infrastructure for the rapid implementation and performance of high-quality Phase II clinical trials to test promising novel pain therapeutics

**Contact:**
Barbara I. Karp, M.D.
Program Director
Early Phase Pain Investigation Clinical Network (EPPIC-Net)

Clinical Coordination Center
- Clinical expertise
- Pain expertise
- Organizes hubs
- Protocol design (with hubs)

Data Coordination Center
- Statistical expertise
- Trial expertise

Repositories:
- Industry and HEAL biosamples and data

~10 Specialized Clinical Centers (hubs + spokes)
- Protocol design (with CCC)
- Trial execution

Candidate therapeutics
- (small molecules, biologics or devices from academia or industry)

Biomarker studies

Deep phenotyping studies

- Data Coordinating Center (U24 Clinical Trials Not Allowed) - RFA-NS-19-024
- Clinical Coordinating Center (U24 Clinical Trial Required) - RFA-NS-19-023
- Specialized Clinical Centers (U24 Clinical Trial Not Allowed) - RFA-NS-19-025
NIH Small Business Programs

**SBIR · STTR**
Small Business Innovation Research
Small Business Technology Transfer

- **Congressionally mandated set-aside (3.65%)**
  - FY 2017: $980M NIH and $55M NINDS

- **For R&D with potential for commercialization**

- **Broad scope:**
  - Therapeutics, diagnostics, tools for research
  - Bench research, translational research, early stage clinical trials

- **Multiple Funding Opportunities:**
  - A majority of our applications are investigator-initiated and come in through the omnibus solicitations
  - Specific funding opportunities for late-stage translational projects and clinical trials

- **Larger budgets for some topics (e.g. animal and clinical studies)**

**Stephanie Fertig M.B.A.** (fertigs@ninds.nih.gov)
• Exploratory Clinical Trials (U01) PAR-18-420 and

• SBIR for Small Business (R44) PAR-18-617
  – Phase 1 and 2 studies of drugs and biologics, feasibility studies of devices, and early studies of surgical, behavioral or rehabilitation therapies.
  – All exploratory trials must contribute to the justification for, and provide some of the data required to inform a future trial to establish efficacy (such as a Phase 3, Phase 4 or Pivotal trial).

• NINDS Efficacy Clinical Trials (U01) PAR-18-422
  – Phase 3, Phase 4 or Pivotal trials

• Dissemination and Implementation Research in Health (R21, R03, R01)
• Clinical Trial Readiness for Rare Neurological and Neuromuscular Disease (U01)
• Comparative Effectiveness Research in Clinical Neurosciences (UG3/UH3)
How to use and access CDE recommendations?

1. View the CDE website tutorial:

2. Visit the Headache CDE landing page:
   https://www.commondataelements.ninds.nih.gov/Headache.aspx#tab=Data_Standards

3. Click on any of the CRF word documents or PDF instrument summaries.

4. Notify NINDSCDE@emmes.com and michael.oshinsky@nih.gov if utilizing the Headache CDEs.
In 2017, there were 70,237 overdose deaths (9.6% higher than 2016)

The prescribed duration of opioid analgesics for acute pain in the primary care setting varies by patient and condition.

For 10 acute pain conditions commonly managed in primary care settings, the probability of obtaining a refill after an initial 7-day opioid analgesic prescription ranged from 11% (headache) to 41% (musculoskeletal injury), with refill probability <25% for most conditions.
Trans-NIH research initiative to:

- Improve prevention and treatment strategies for opioid misuse and addiction
- Enhance pain management

Goals are scientific solutions to the opioid crisis

Coordinating with the HHS Secretary, Surgeon General, federal partners, local government officials and communities

www.nih.gov/heal-initiative
Helping to End Addiction Long-term
HEAL Initiative: At a glance

– **$500M/year Trans - NIH effort starting FY2018**
  • Over $850M to be obligated in FY2019

– **12 NIH Institute and Centers leading 26 HEAL research projects**
  • Over 20 collaborating Institutes, Centers and Offices
  • From prevention research, basic and translational research, clinical trials, to implementation science
  • Multiple projects integrating research into new settings
    – e.g. health care, criminal justice, Medicare populations etc.

– **Released 40+ funding announcements for FY2019**
Platform Screening Program for Pain (PSPP) Mission and Strategy

Accelerate the Discovery and Pre-Clinical Development of Non-Addictive Treatments for Pain

Contact:
Smriti Iyengar, Ph.D., Program Director
Sarah Woller, Ph.D., Project Manager

• Goal: engineer a preclinical testing platform to identify and profile non-addictive therapeutics for pain

Small molecules
Biologics
Devices
Natural products

PSPP

Successful compounds / devices move toward clinical trials
Biomarkers Significantly Improve the Probability of Successful Therapeutic Development

**Success Rates of Pain Drugs Compared to Drugs For All Other Diseases**

Therapeutic Development Success Rates for Pain Therapeutics Are Lower Than Other Disease Indications

**Biomarkers Significantly Improve the Probability of Successful Therapeutic Development**

**Overall Phase Success Rates**

<table>
<thead>
<tr>
<th>Phase</th>
<th>New Molecular Entity (NME)</th>
<th>All Diseases</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>57%</td>
<td>63%</td>
</tr>
<tr>
<td>Phase II</td>
<td>16%</td>
<td>31%</td>
</tr>
<tr>
<td>Phase III</td>
<td>39%</td>
<td>58%</td>
</tr>
<tr>
<td>NDA/BLA</td>
<td>56%</td>
<td>85%</td>
</tr>
<tr>
<td>Phase I to Approval</td>
<td>2%</td>
<td>9.6%</td>
</tr>
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**Probability of Success With or Without Selection Biomarkers**

<table>
<thead>
<tr>
<th>Phase I to Phase II</th>
<th>Phase II to Phase III</th>
<th>Phase III to NDA/BLA</th>
<th>NDA/BLA to Approval</th>
<th>Phase I to Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Biomarkers</td>
<td>63%</td>
<td>28%</td>
<td>55%</td>
<td>8.4%</td>
</tr>
<tr>
<td>With Selection Biomarkers</td>
<td>76%</td>
<td>46%</td>
<td>76%</td>
<td>94%</td>
</tr>
<tr>
<td>94%</td>
<td>83%</td>
<td>76%</td>
<td>94%</td>
<td>25.9%</td>
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**Mary Ann Pelleymounter, PhD**

**Program Director**

mary.pelleymounter@nih.gov
HEAL Biomarker Initiative: Discovery and Validation of Biomarkers, Endpoints, and Signatures for Pain Conditions

**Program Goal:** Develop Objective Biomarkers and Endpoints To Facilitate Discovery of New Non-Addictive Treatments for Pain

**Discovery of Biomarkers, Biomarker Signatures, and Endpoints for Pain**

**RFA-NS-18-041** – R61/R33  
Will facilitate the discovery of robust biomarkers, biomarker signatures and objective endpoints for pain conditions for use in clinical trial design and clinical practice

**Analytical and/or Clinical Validation of a Candidate Biomarker for Pain**

**RFA-NS-18-046** – R61/R33  
Will support the analytical and clinical validation of candidate biomarkers for use in the discovery and development of non-opiate alternatives to the treatment of pain conditions using retrospective and/or prospective methods

**Remaining Application Due Dates:**
- November 25, 2019;  
- March 12, 2020

For more information about the HEAL Initiative:  
[https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative](https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative)
HEAL - Discover and Validate Novel Targets for Safe and Effective Pain Treatment

To promote the basic science discovery and validation of targets for the treatment of pain that can be used to develop treatments that have minimal side effects and little to no abuse/addiction liability

Basic biology target discovery projects
- Encourage collaboration from other fields
- Designed to reveal novel targets for small molecules, natural products, biologics, devices
- Devices: discovery of new sites for stimulation or electrophysiological signatures
- Open to all pain systems in CNS or periphery

Pain target validation
- Novel in vitro/ex vivo assays
- Animal model systems development
- Multidisciplinary tools
- Multisite validation; robustness; reproducibility
- Validation of pharmacodynamic and predictive biomarkers

Due Dates: November 12, 2019

RFA-NS-18-043 – R01
RFA-NS-18-042 – R21

Translating Discoveries into Effective Devices for Pain Treatment

Reduce reliance on opioids through the enhanced targeting and reduced invasiveness of diagnostic and therapeutic devices to manage pain

Funding Opportunities

- Translational Devices to Treat Pain (UG3/UH3 Clinical Trial Optional) - RFA-NS-19-016
- Translational Devices to Treat Pain (U44 Clinical Trial Optional) - RFA-NS-19-017
- Clinical Devices to Treat Pain (UH3 Clinical Trial Optional) - RFA-NS-19-018
- Stimulating Peripheral Activity to Relieve Conditions (SPARC): Anatomical and Functional Mapping of Pain-Related Visceral Organ Neural Circuitry (U01 Clinical Optional) - RFA-RM-19-001
- Translational Development of Devices to Treat Pain (U18 Clinical Trial Not Allowed) - RFA-EB-18-003

https://www.nibib.nih.gov/devices_for_pain
Support development, optimization, and translational activities and small clinical studies involving therapeutic and diagnostic devices for disorders that affect the nervous or neuromuscular systems.

**Neural Devices**

- **Device Optimization**
- **Pre-IDE Studies**
- **Early Feasibility Studies / Clinical Trials**

**Bioengineering Research Partnerships**
(U01) (PAR-18-208)

**Translational Neural Devices**

**BRAIN Device Optimization**
(U01) (RFA-NS-18-019)

**BRAIN Next-Generation Devices**

**BRAIN Next-Generation Devices**
(UH3) (RFA-NS-18-023)
Speak to Program Staff and Send Us Your Applications!

Questions:
Michael.Oshinsky@nih.gov