NIH/NINDS Opportunities for Pain and Migraine Research

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Division of Clinical Research Programs

Clinical Trial Readiness	Phase I First in Human	Phase Ib First in target population	Phase IIa Proof of Concept (Biomarker)	Phase IIb Preliminary Efficacy (Clinical)	Phase III Definite Efficacy	Phase IV Post Marketing Surveillance	Dissemination Implementation CER

PAR CT Readiness

PAR Exploratory Clinical Research

Cooperative Programs in Clinical Research PAR Phase II/III CTs

SIREN

NeuroNEXT

StrokeNet

HEAL EPPIC-NET

PAR Dissemination Implementation

PAR Comparative Effectiveness

Biomarker Discovery/Validation

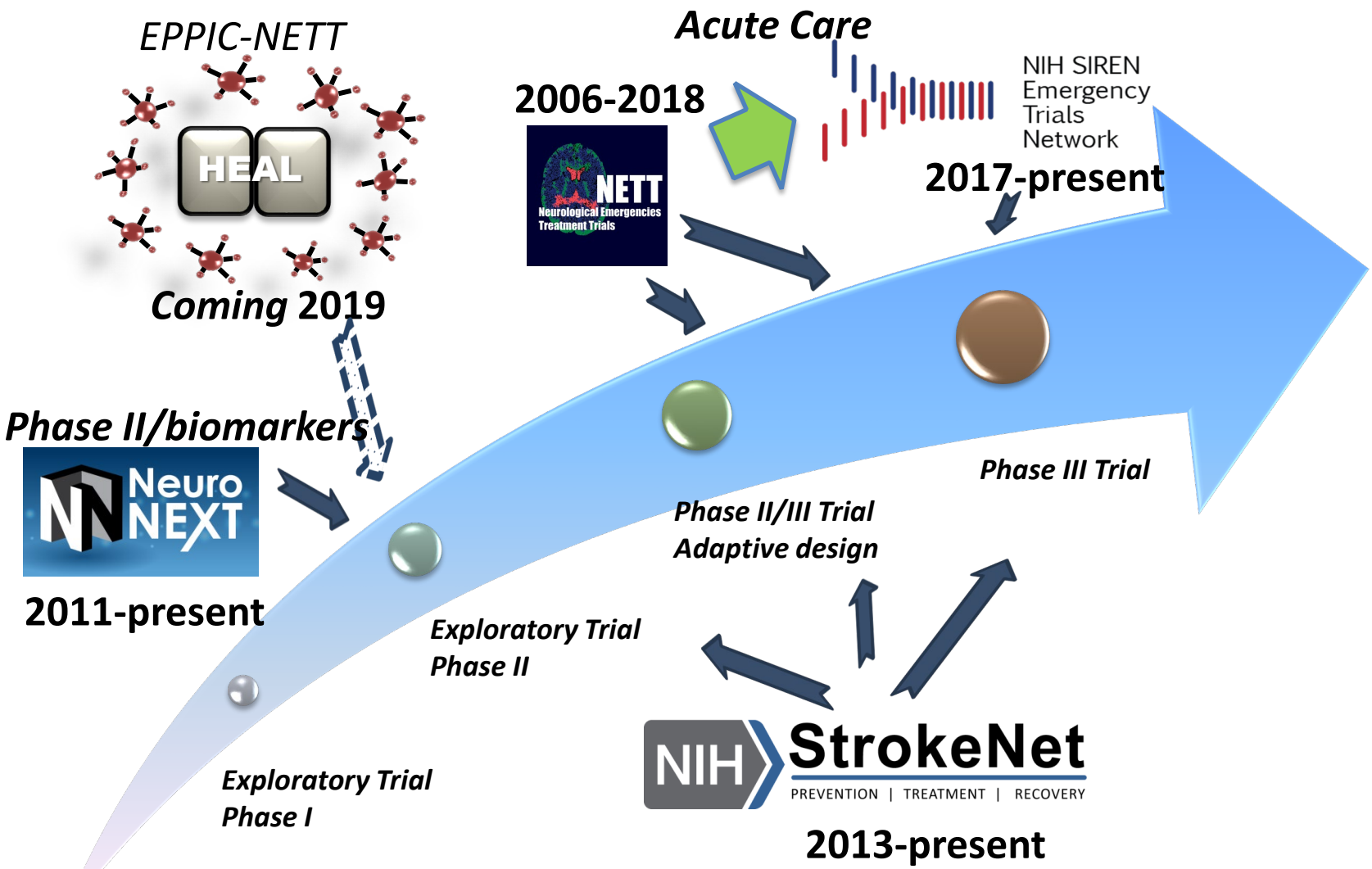
Outcome Discovery/Validation

Clinical Trial Embedded Natural History Studies

Common Data Elements

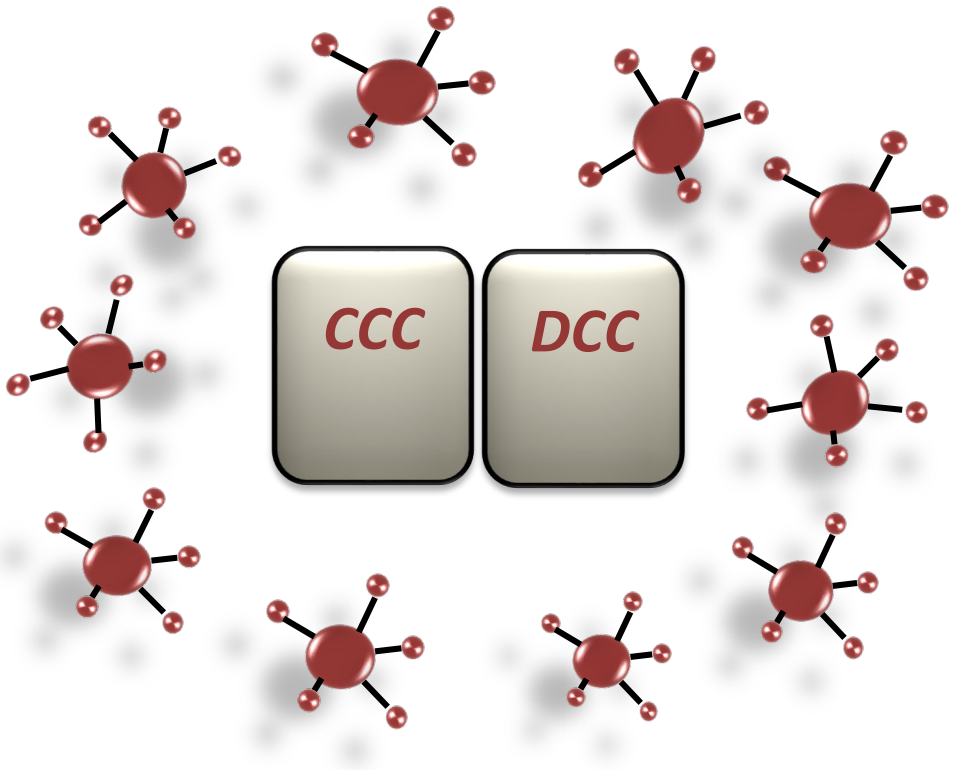
NIH
National Institutes of Health

NINDS Clinical Trial Networks



NINDS Networks

HEAL: NINDS Early Phase Pain Investigation Clinical Network (EPPIC-NETT)



Contact:

Barbara I. Karp, M.D.
Program Director

National Institute of Neurological Disorders and Stroke

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***

Early Phase Pain Investigation Clinical Network (EPPIC-Net)

FNIH
Foundation for the National Institutes of Health

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

Biomarker studies

Deep phenotyping studies

Clinical Coordination Center

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

Data Coordination Center

- Statistical expertise
- Trial expertise

Repositories: Industry and HEAL bio-samples and data

~10 Specialized Clinical Centers (hubs + spokes)

- Protocol design (with CCC)
- Trial execution

- 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 National Institute of Neurological Disorders and Stroke

NIH Small Business Programs

SBIR · STTR
America's Seed Fund

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)

Division of Clinical Reseach Funding Opportunities

- **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)**

NIH
National Institutes of Health

NINDS Supports Clinical Headache Research

PROJECT OVERVIEW CDE SEARCH CRF SEARCH FORM BUILDER CONTACT

NINDS Common Data Elements

Harmonizing Information. Streamlining Research.

▼ CDEs ▼ Tools ▼ Learn

CDEs Now Available:
- Headache (Version 2.0)
- Sports-Related Concussion
- Unruptured Cerebral Aneurysms and Subarachnoid Hemorrhage

Are you using the NINDS CDEs?
- Citing CDE Usage
- Let us know through our Feedback Form

Learn to Use the CDEs:
- Study Start-Up Tutorial

CDEs > Headache

Headache

Data Standards | Overview | History and Acknowledgements | References | Updates | Feedback and Suggestions

The National Institute of Neurological Disorders and Stroke (NINDS), other Federal agencies, and international organizations have the common mission of developing data standards for clinical research. Through the efforts of subject-specific working groups, topic-driven data elements have been created. The first set of Common Data Elements (CDEs) for Headache were developed in 2011. In June 2017, the Headache CDE Working Group finished their work on version 2.0 of the Headache CDEs. The Core and Supplemental-Highly Recommended CDEs to be used by an investigator when beginning a research study in Headache are listed in the Start-up Resource Listing Start-up Resource Listing.

Many of the CDEs will overlap across study types, which allows for comparisons and meta-analyses across studies. Consistency of the data elements and the CDE formats are kept in order to ensure the ability to transfer critical medical information electronically from one center to another. This consistency also allows for continuity across different disease areas. The goals of the NINDS CDE initiative are to increase the efficiency and effectiveness of clinical research studies and clinical treatment, increase data quality, facilitate data sharing and help educate new clinical investigators.

Organized by domains and sub-domains, often used in clinical studies, data standards include:

- **CDEs** - Classified as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory
- **CRF Modules** - logically organize CDEs for data collection
- **Guidelines** - to provide further information about the CDEs.

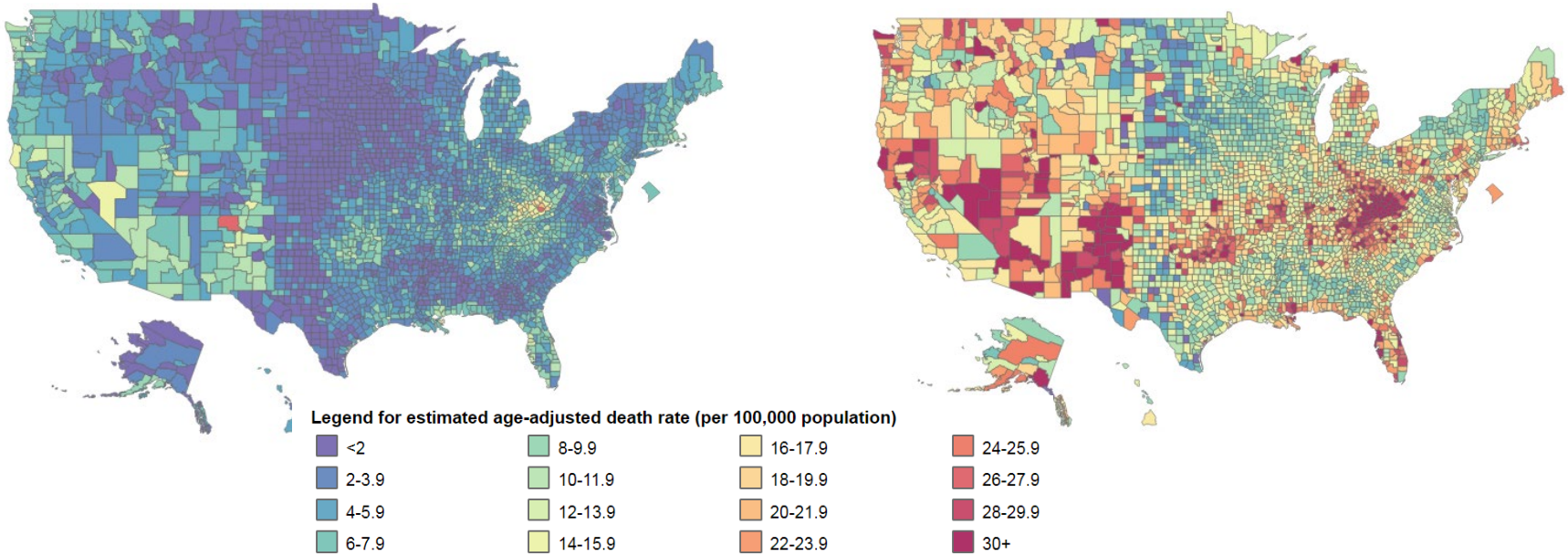
How to use and access CDE recommendations?

1. ***View the CDE website tutorial: https://www.commondataelements.ninds.nih.gov/Tutorials.aspx***
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.***

https://www.commondataelements.ninds.nih.gov/Headache.aspx

The Opioid Crisis: National Overdose Death Rates

In 2017, there were 70,237 overdose deaths (9.6% higher than 2016)



Source: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Search

Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Days' Supply of Initial Opioid Analgesic Prescriptions and Additional Fills for Acute Pain Conditions Treated in the Primary Care Setting — United States, 2014

Weekly / February 15, 2019 / 68(6);140–143

Mallika L. Mundkur, MD[1]; Jessica M. Franklin, PhD[2]; Younathan Abdia, PhD[2]; Krista F. Huybrechts, PhD[2]; Elisabetta Patorno, MD, DrPH[2]; Joshua J. Gagne, PharmD, ScD[2]; Tamra E. Meyer, PhD[1]; Judy Staffa, PhD[1]; Brian T. Bateman, MD[2] (View author affiliations)

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.

https://www.cdc.gov/mmwr/volumes/68/wr/mm6806a3.htm

The Response:
Helping to End Addiction Long-term (HEAL) Initiative

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

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***

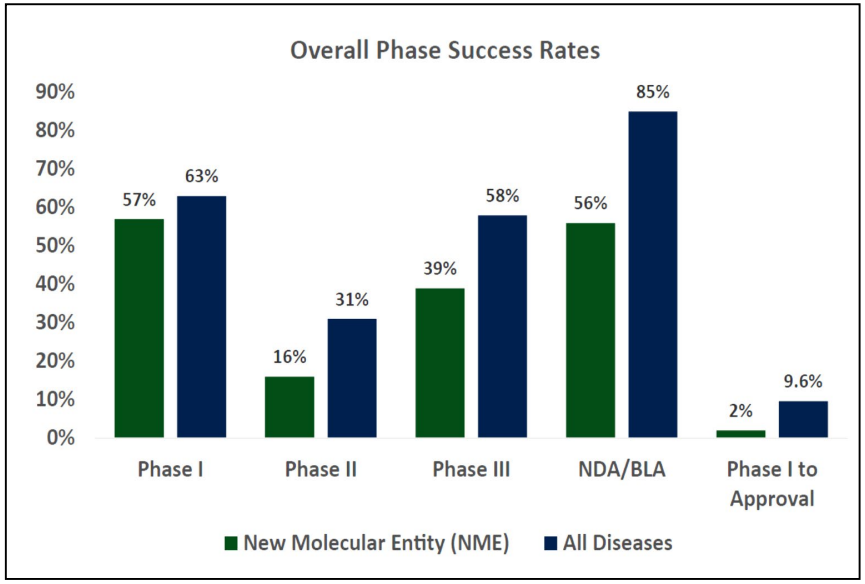
NIH National Institute of Neurological Disorders and Stroke

HEAL Pain Biomarker Program at NIH

Collaborative Effort Between NINDS, NCI, NEI, NIDDK, NICHD, NIA, NIAAA, NIDA, NIAMS, NIBIB, NIDCR, NINR, NCATS, NLM, NCCIH

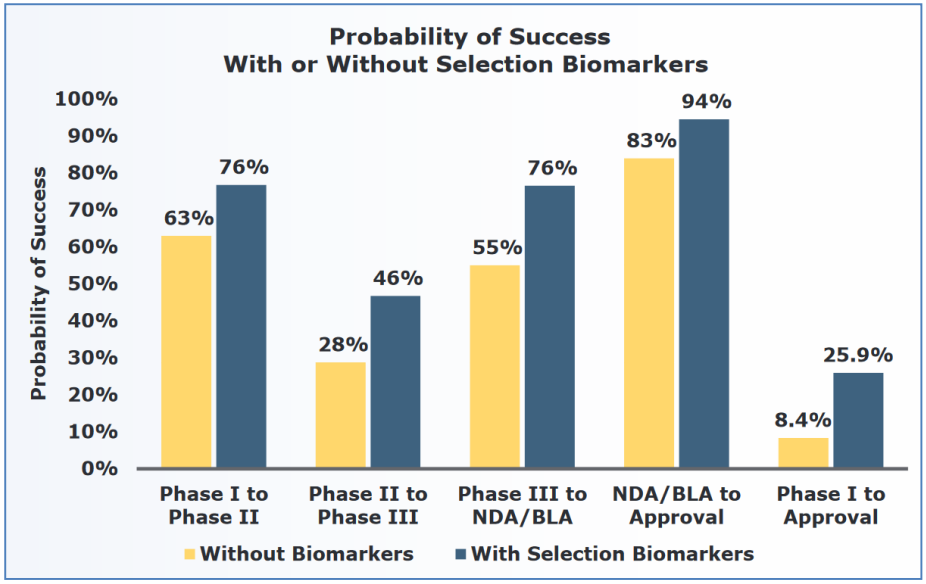
Success Rates of Pain Drugs Compared to Drugs For All Other Diseases

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



Thomas, D and Wessel, C., Pain and Addiction Therapeutics, Biotechnology Innovation Organization, February, 2018

Biomarkers Significantly Improve the Probability of Successful Therapeutic Development



Thomas D.W., Burns J., Audette J., Carroll A, Dow-Hygelund C, Hay, M, Clinical Development Success Rates 2006-2015, Bio-Industry Analysis

Mary Ann Pelleymounter, PhD

Program Director

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NIH National Institute of Neurological Disorders and Stroke

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

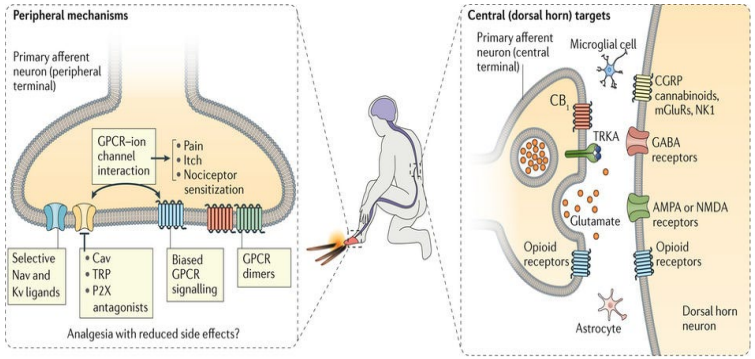
Remaining Application Due Dates:
- November 25, 2019;
- March 12, 2020

For more information about the HEAL Initiative:
https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative

NIH National Institute of Neurological Disorders and Stroke

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



Nat Rev Drug Discov. 2017 Aug;16(8):545-564.

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

Due Dates: November 12, 2019

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*

Previously identified targets

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*

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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

Brain Research through Advancing Innovative Neurotechnologies

Stimulating Peripheral Activity to Relieve Conditions

NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund

NIH National Institute of Biomedical Imaging and Bioengineering

NIH National Institute of Neurological Disorders and Stroke

https://www.nibib.nih.gov/devices_for_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

Neural Devices

Support development, optimization, and translational activities and small clinical studies involving therapeutic and diagnostic devices for disorders that affect the nervous or neuromuscular systems

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

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

Translational Neural Devices
(UG3 / UH3 / U44) (RFA-NS-18-011 / RFA-NS-18-012)

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

BRAIN Next-Generation Devices
(UG3 / UH3 / U44) (RFA-NS-18-021 / RFA-NS-18-022)

BRAIN Next-Generation Devices
(UH3) (RFA-NS-18-023)

Speak to Program Staff and Send Us Your Applications!

Questions:

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