NIH · Helping to End Addiction Long-term

National Institutes of Health
Turning Discovery Into Health

National Institute of Neurological Disorders and Stroke

Review of NIH Programs for Developing and Testing Pain Treatments

HEAL Partnership Committee Meeting

March 5, 2019

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH HEAL Initiative: Priorities for Enhancing Pain Management

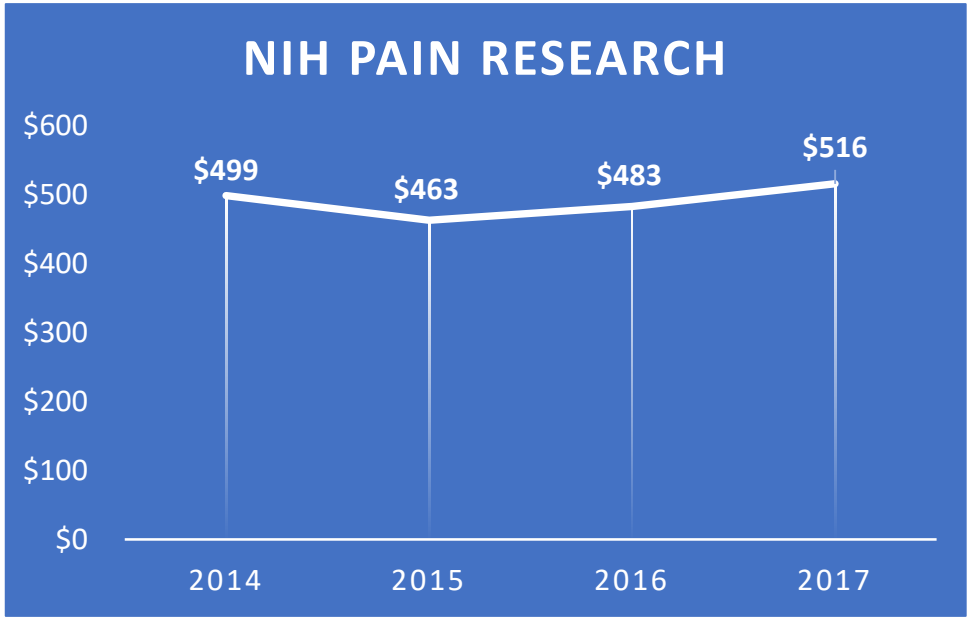
- Understand the biological underpinnings of chronic pain
- Accelerate the discovery and pre-clinical development of non-addictive pain treatments
- Advance new non-addictive pain treatments through the clinical pipeline
- Establish the best pain management strategies for acute pain and numerous chronic pain conditions

Read about the 2019 research plan:

www.nih.gov/heal-initiative

NIH Investment in Pain Research Before HEAL

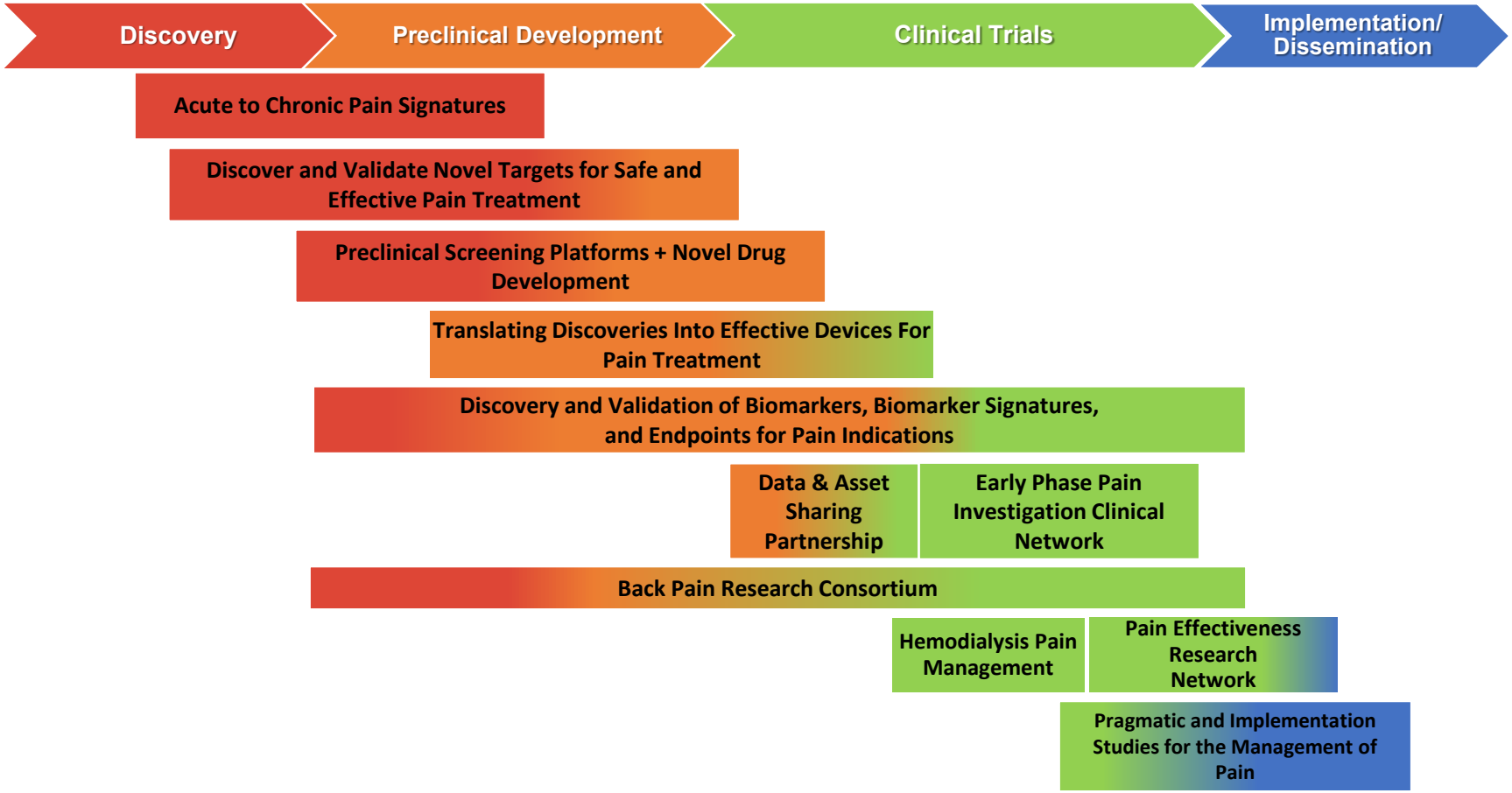
In 2017, NIH invested $516 million on pain research



Pain cuts across all 27 NIH Institutes and Centers

The NIH Pain Consortium was established with the goal of enhancing pain research and promoting collaboration across NIH

HEAL Programs for Pain Cover the Research Spectrum

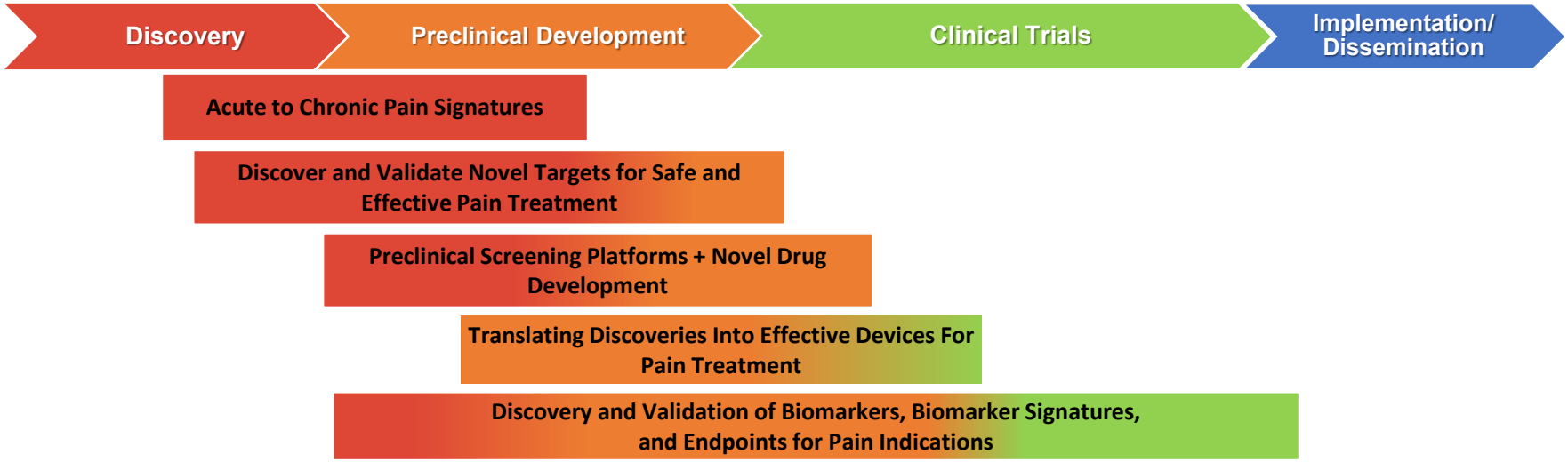


Understand the biological underpinnings of chronic pain

Understand the biological underpinnings of chronic pain

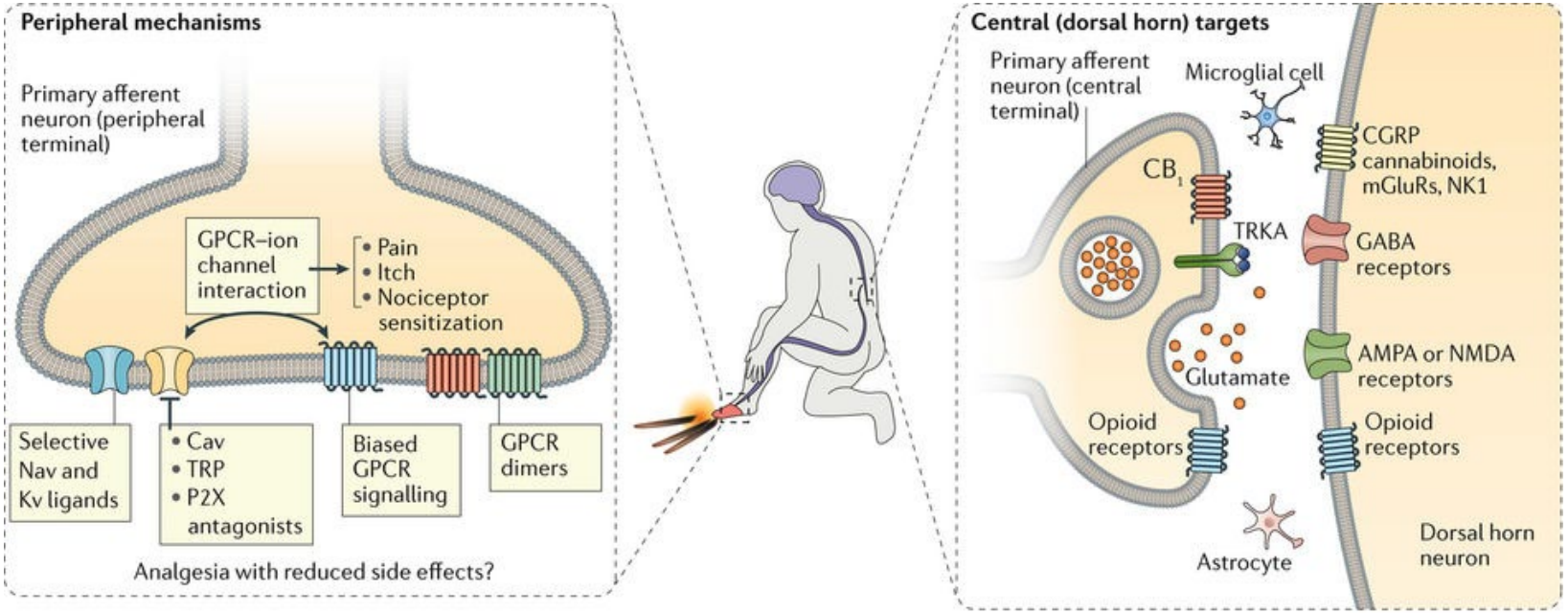
- Acute to Chronic Pain Transitions Program
- Objective biosignatures to identify susceptibility or resilience to chronic pain
    - Phenotyping, genotyping, sensory tests, imaging, -omics
- Prevention Outcomes
    - Mechanisms; Novel therapeutic targets
    - Cohort stratification
        - Risk of chronic pain
        - Risk of long term opioid use
- Structure: Clinical Coordination Center, Clinical Centers, Omics Data Generation Centers, Data Integration and Resource Center
- Awards expected Spring 2019

Accelerate the discovery and pre-clinical development of non-addictive pain treatments



Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- To promote the basic science discovery and validation of **novel 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.

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- **Target Discovery**
  - For small molecules
    - Channels, lipids, enzymes
  - For biologics
    - Peptides, cell-based therapies, antibodies
    - DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technique
  - For devices
    - Nerves for neuromodulation devices, electrophysiological signatures of pain, sites for combination pumps
- Projects also include a strong rationale and/or experiments to demonstrate that the target does not pose a significant abuse liability

RFA-NS-18-043 – R01
RFA-NS-18-042 – R21
NOT-NS-18-073 – Administrative Supplements

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

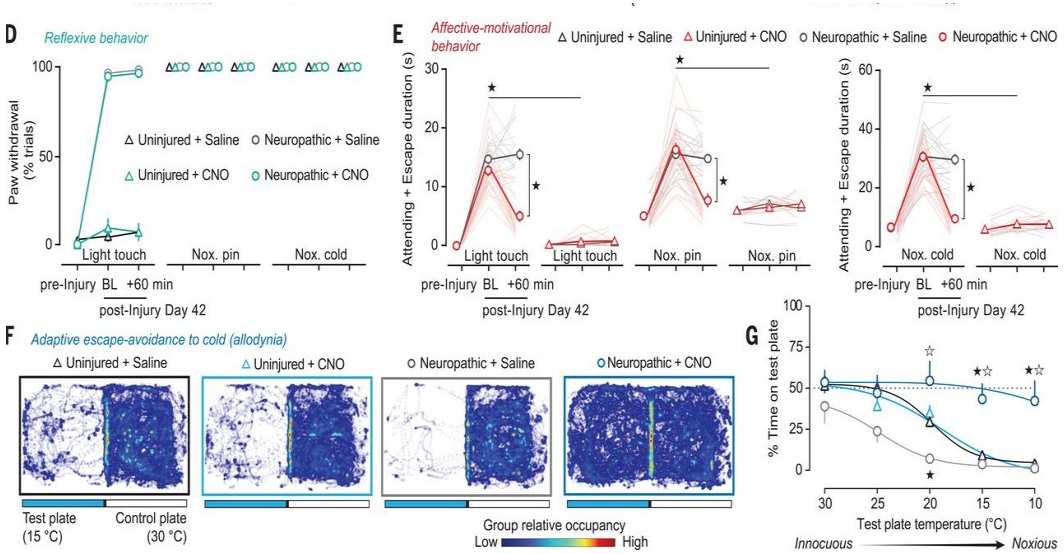
Brain Research through Advancing Innovative Neurotechnologies

Stimulating Peripheral Activity to Relieve Conditions

- Leverage ongoing mapping / target discovery activities in BRAIN, SPARC, and other HEAL Initiatives
- Late stage device development
- Verification and validation to accelerate regulatory approval
- Early clinical studies to de-risk new and improved pain treatments

Translating Discoveries into Effective Devices for Pain Treatment

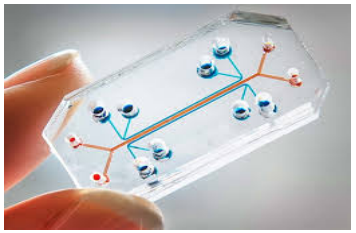
An Amygdalar Neural Ensemble Encodes the Unpleasantness of Pain
Corder G, Ahanonu B, Grewe BF, Wang D, Schnitzer

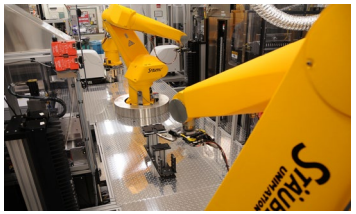


- Can BRAIN Initiative science translate circuit activity into an assay for developing non addictive therapeutics?
  - Silencing BLA neurons in people with chronic low back pain?

Human Cell-based Screening Platforms and Novel Drugs to Treat Pain, Addiction, and OD

- Support preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapies to treat pain
- Develop human cell/tissue models
  - Peripheral and central nervous system
  - Normal and disease states
  - iPSC-derived neurons, 3D printed organoids, tissue chips
- Advance investigational drugs for new targets
  - Human tissue constructs to identify new probes/drug leads
  - Automated chemical synthesis
  - Artificial Intelligence to identify new chemical structures
  - IND-enabling studies: Optimization of Non-addictive Therapies [Small Molecules and Biologics] to Treat Pain

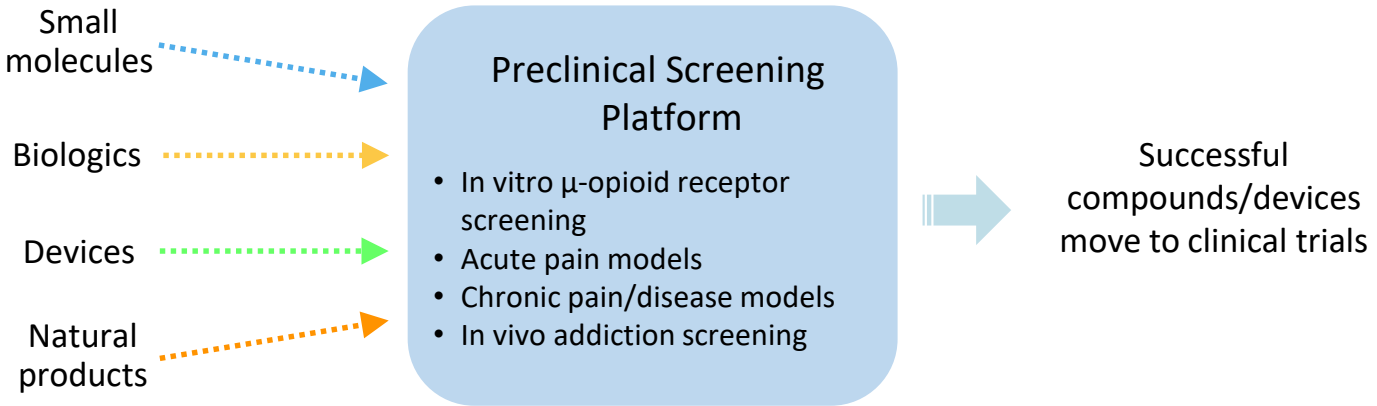




RFA-NS-19-010
RFA-NS-19-020
(SBIR)

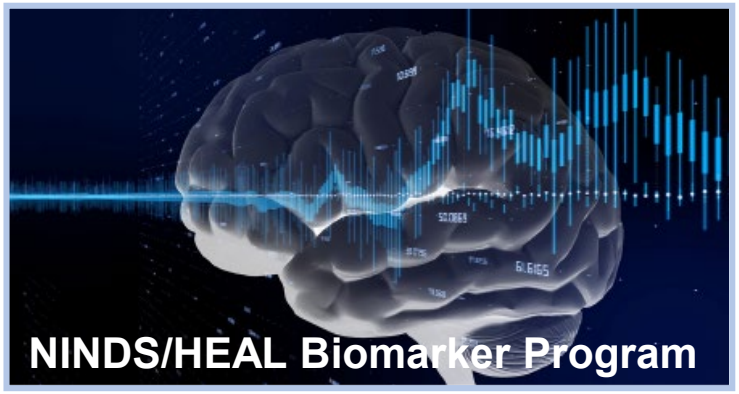
Preclinical Screening Platform for Pain (PSPP)

- Establish a one-stop preclinical testing platform that promotes the testing and characterization of non-addictive modalities for the treatment of pain
- Incentivize academia & industry to accelerate discovery of non-addictive, effective therapies
- Develop or refine animal models of pain conditions-available to research community
- Generate high quality data to support partnerships, translational programs
- Provide access to research community

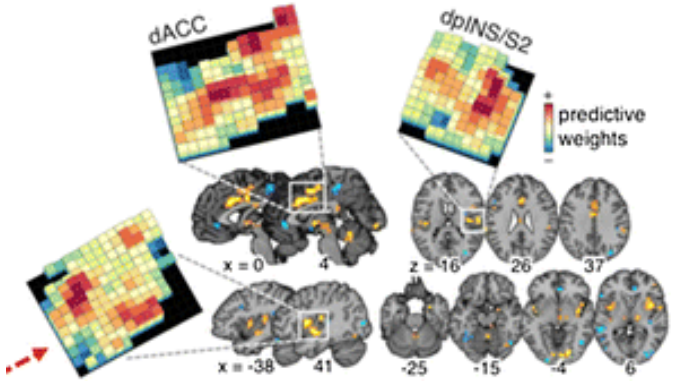


Discovery and Validation of Biomarkers, Endpoints and Signatures for Pain Conditions

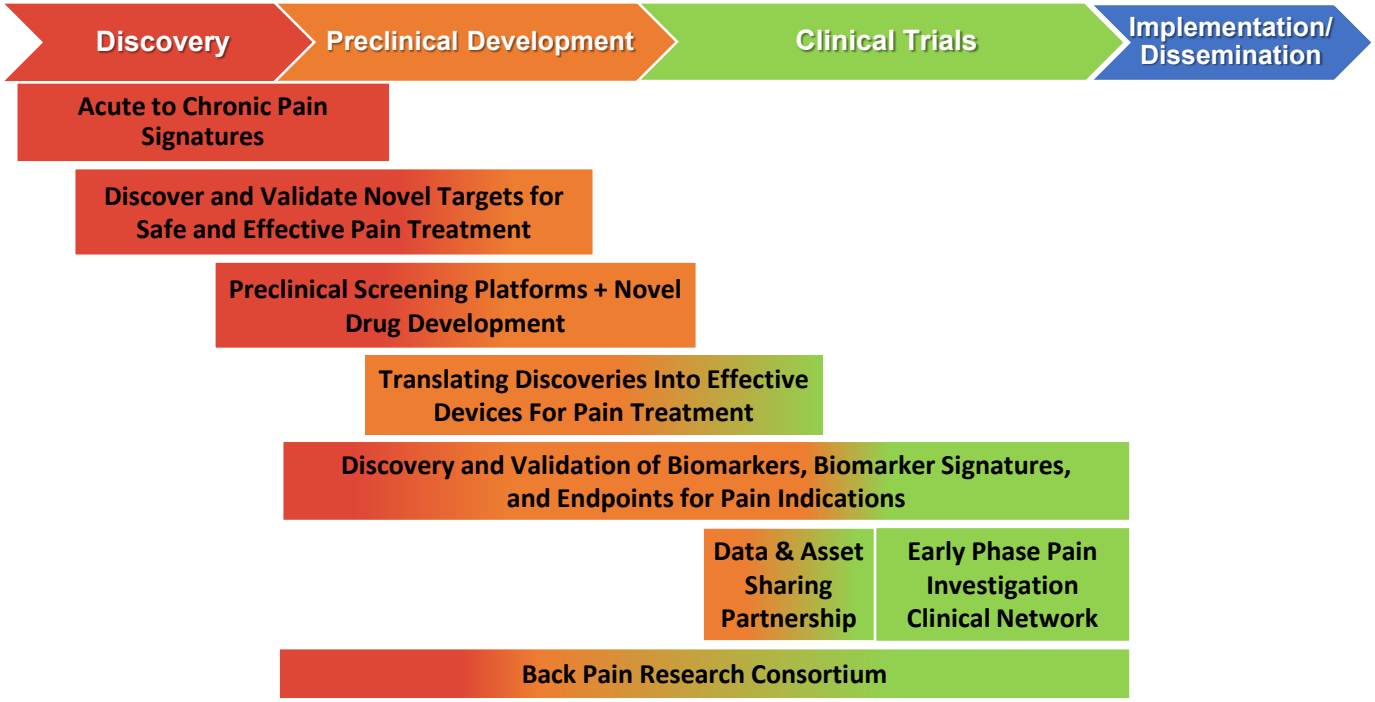
- Goal: facilitate the discovery and development of high-quality biomarkers to accelerate the development of non-addictive therapeutics for the treatment of pain conditions
- Advanced analytical and clinical validation of pain biomarkers, biomarker signatures, and/or endpoints using retrospective and/or prospective methods: RFA-NS-18-046
- Identification and initial biological, analytical and clinical validation of pain biomarkers, biomarker signatures, and/or endpoints: RFA-NS-18-041



16 Institutes and Centers



HEAL Programs for Pain Cover the Research Spectrum



Early Phase Pain Investigation Clinical Network + Data and Asset Sharing Partnership

Improve quality, consistency, efficiency of early phase pain clinical trials

- EPPIC-net will test compounds and devices judged highly meritorious in peer review that come from industry and academia
- Clinical Coordination Center, Data Coordination Center, 10 specialized clinical sites (hub and spoke design)
- Incentivize, accelerate Phase II trials
- Focus on well-defined pain conditions with high-unmet need
- Reduce the time to start, enroll, run, and complete trials
- Incorporate biomarker studies
- Accommodate platform trial designs

Data and Asset Sharing Partnership

- EPPIC-net Data Coordination Center will host data and biosample repositories from HEAL programs and industry partners
- FNIH and the HEAL Partnership Committee will encourage submission of assets for phase 2 clinical trials

FNIH
Foundation for the National Institutes of Health

More info coming later today!

Early Phase Pain Investigation Clinical Network (EPPIC-Net) Mission and Goals

Mission: To improve the treatment of acute and chronic pain and reduce the reliance on opioids, by accelerating the early phase testing of promising non-addictive therapeutics and devices to relieve pain

Goals

- Develop a highly effective infrastructure for the rigorous early phase testing of promising pain treatments (small molecules, biologics, devices) from academia and industry.
  - Take advantage of existing pain expertise in both academia and industry
  - Advance pain clinical research though a learning network
  - Train new clinical investigators,
  - Design and test innovative clinical trial paradigms,
  - Establishing well-phenotyped patient cohorts (e.g. BACPAC),
- Incorporate biomarkers of target engagement or proof-of-principle into clinical trial design for new non-addictive pain treatments whether small molecules, devices, or biologics

EPPIC-Net Infrastructure

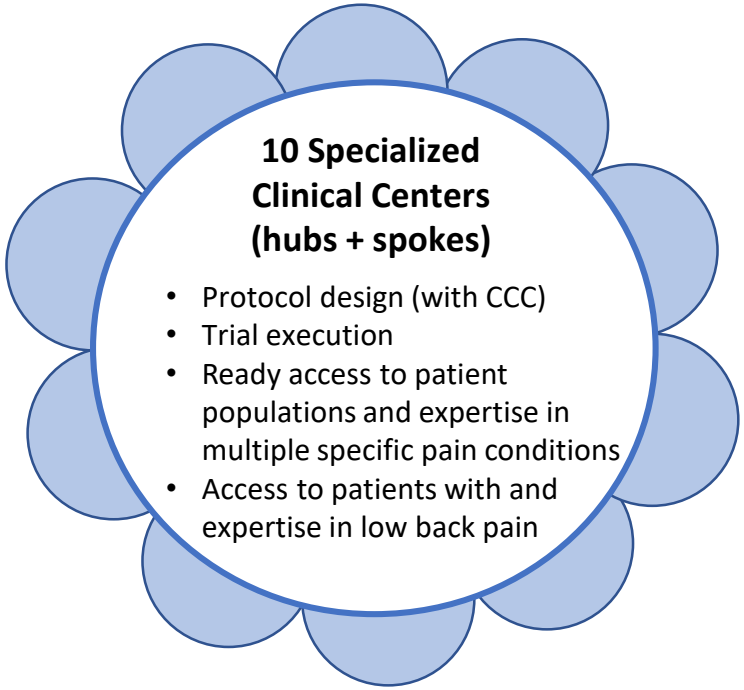
Data Coordination Center

- Statistical expertise
- Trial expertise

Repositories:
Industry and HEAL biosamples, neuroimaging, and data

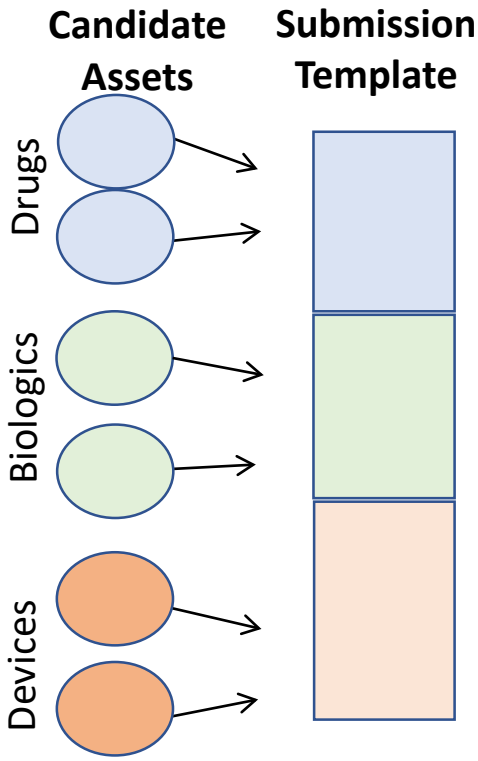
Clinical Coordination Center

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



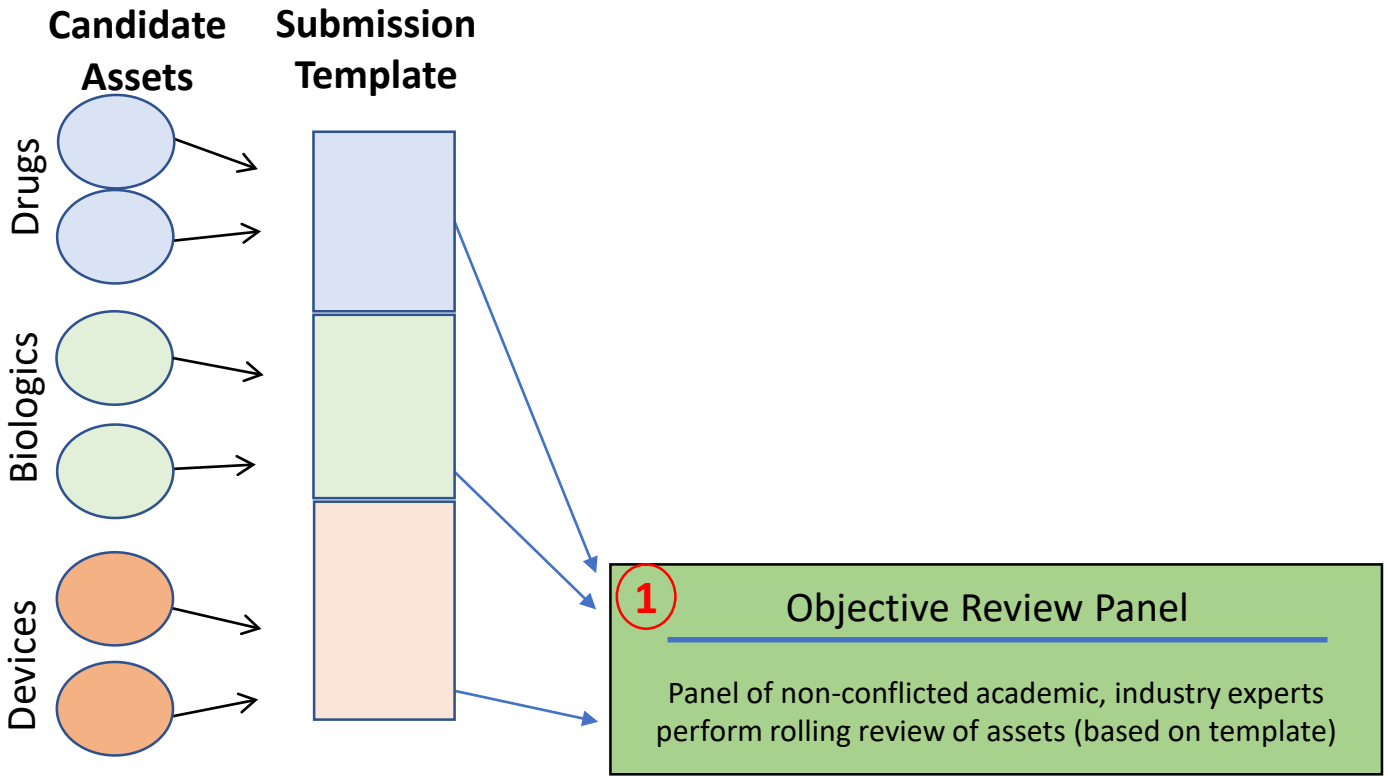
Coordination centers and clinical sites all solicited through funding opportunities, planned to award at May council

EPPIC-Net Process: Asset Submission

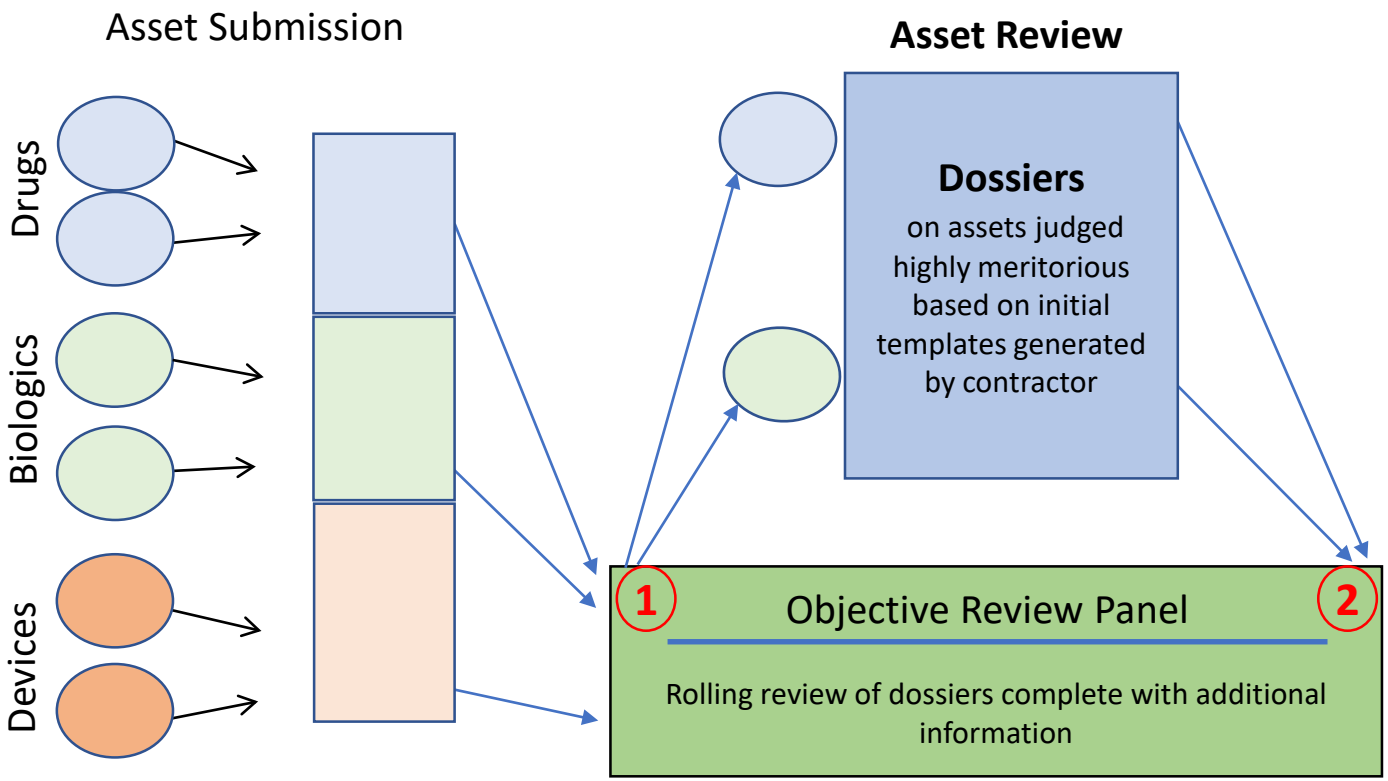


- Basic information on asset to be entered into submission template
  - Specialized for small molecules, biologics and devices
- Draft template(s) are being developed now by NINDS, **with FDA**, and will go to **HEAL Partnership Committee for input**
  - Contents include: e.g., asset type, completed clinical and preclinical studies, pain type, competing products, primary outcomes
- Template submission will be **open to anyone** and **available online**
- **Outreach to Submitters**:
  - Academic networks: e.g., NIH Guide Notice, listservs, blogs
  - Connections through partners on HEAL Partnership Committee: PhRMA, BIO, AdvaMed
- The whole process will occur with use of **Other Transaction Authority**

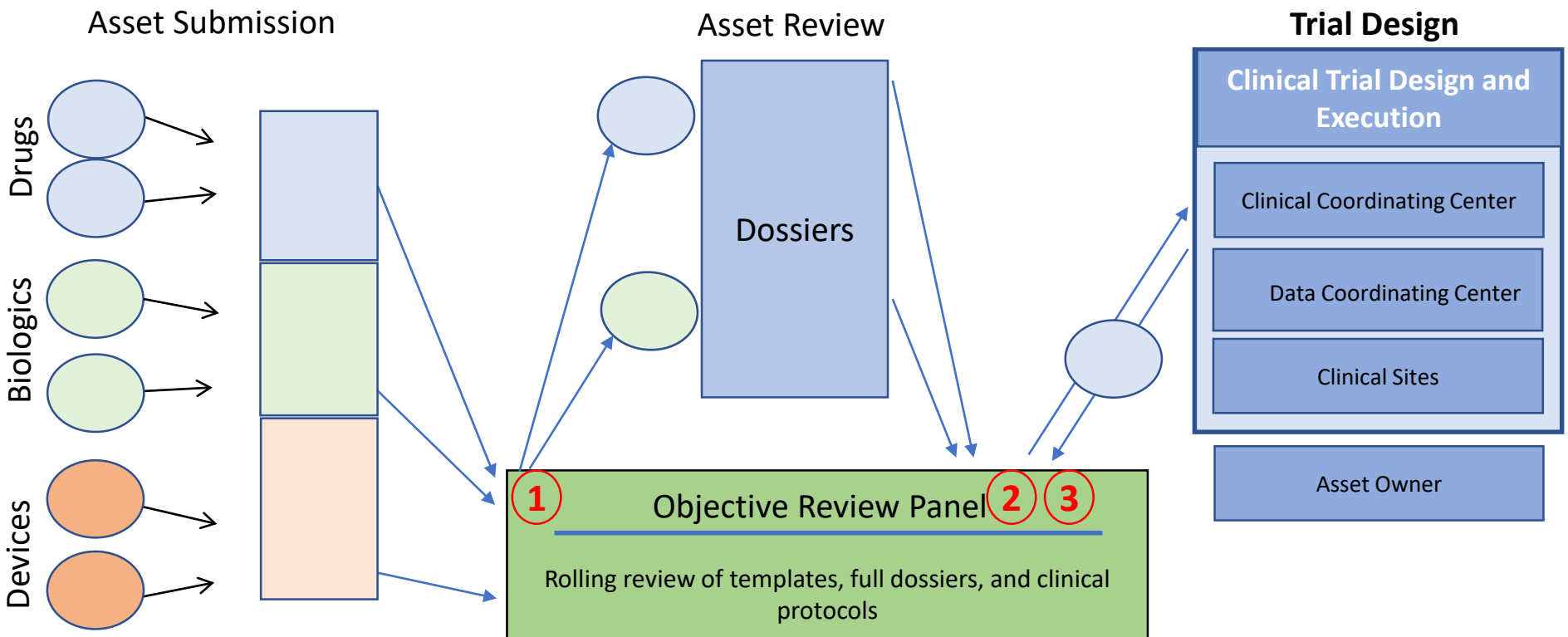
EPPIC-Net Process: Templates + Review #1



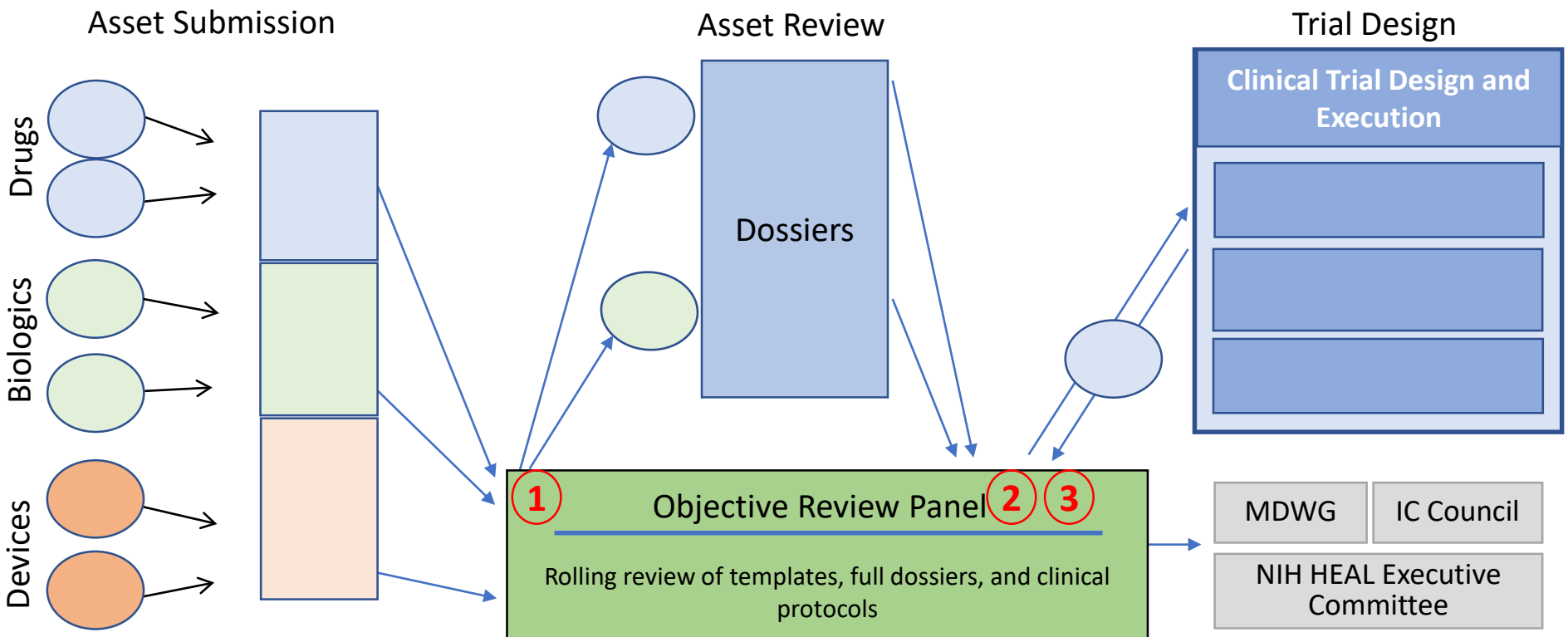
EPPIC-Net Process: Dossiers + Review #2



EPPIC-Net Process: Asset to Clinical Trial Protocol + Review #3

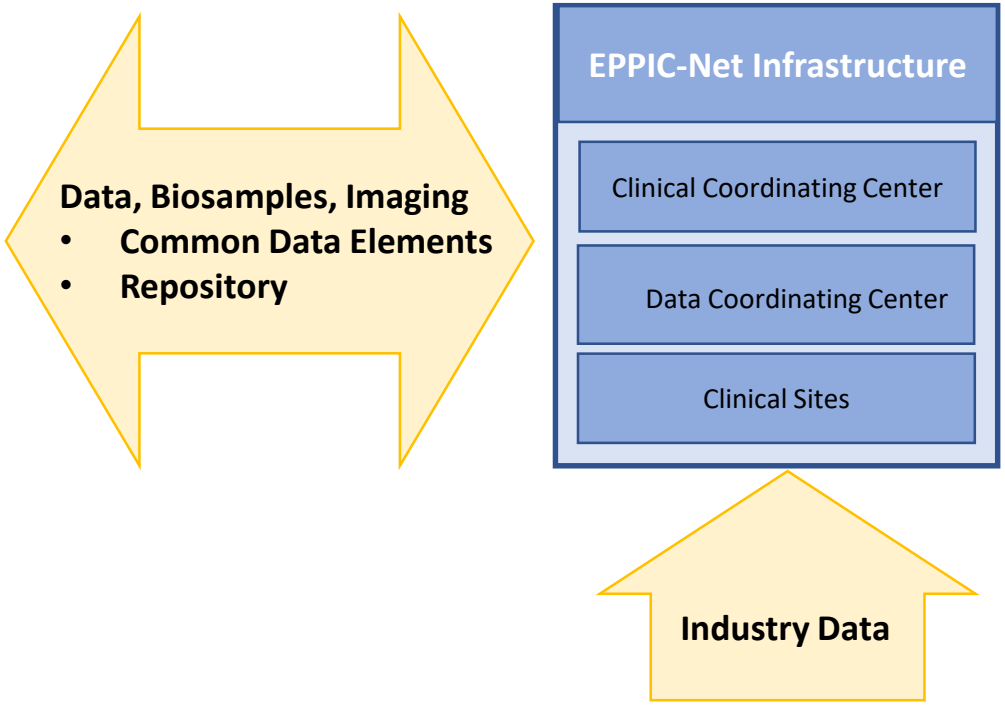


EPPIC-Net Process: NIH and Council Review



EPPIC-NET Resources for other HEAL Projects

- Back Pain Research Consortium BACPAC
- Pain Management Effectiveness Research Network
- Pain Biomarkers Initiatives
- Common Fund: Acute to Chronic Pain Signatures
- Pragmatic and Implementation Studies for the Management of Pain (PRISM)
- Integrated Approach to Pain & Opioid Use in Hemodialysis Patients
- Other Pain Preclinical Programs



EPPIC-Net Process and Timing

- Awards for CCC and DCC infrastructure
  - Receipt date: February 6, 2019 (passed)
  - Tentative Review date: April 15, 16
  - Tentative MDWG review: Mid-May
  - Tentative Council approval: May 23-24
- Awards for Clinical Centers (hubs and spokes)
  - Dates same as above, but considering additional receipt/review dates

- OTA awards for clinical trials
- Rolling submission; anticipate first trials in FY2020

Back Pain Research Consortium: BACPAC

Back Pain Consortium (BACPAC) Research Priorities
A patient-centric, translational research program

BASIC: Integrated model of Low Back Pain through improved understanding of mechanisms, leading to new therapies

TRANSLATIONAL: Clinical trails, integrating new therapies into multimodal interventions, combined with deep phenotyping and patient-reported symptoms and outcomes

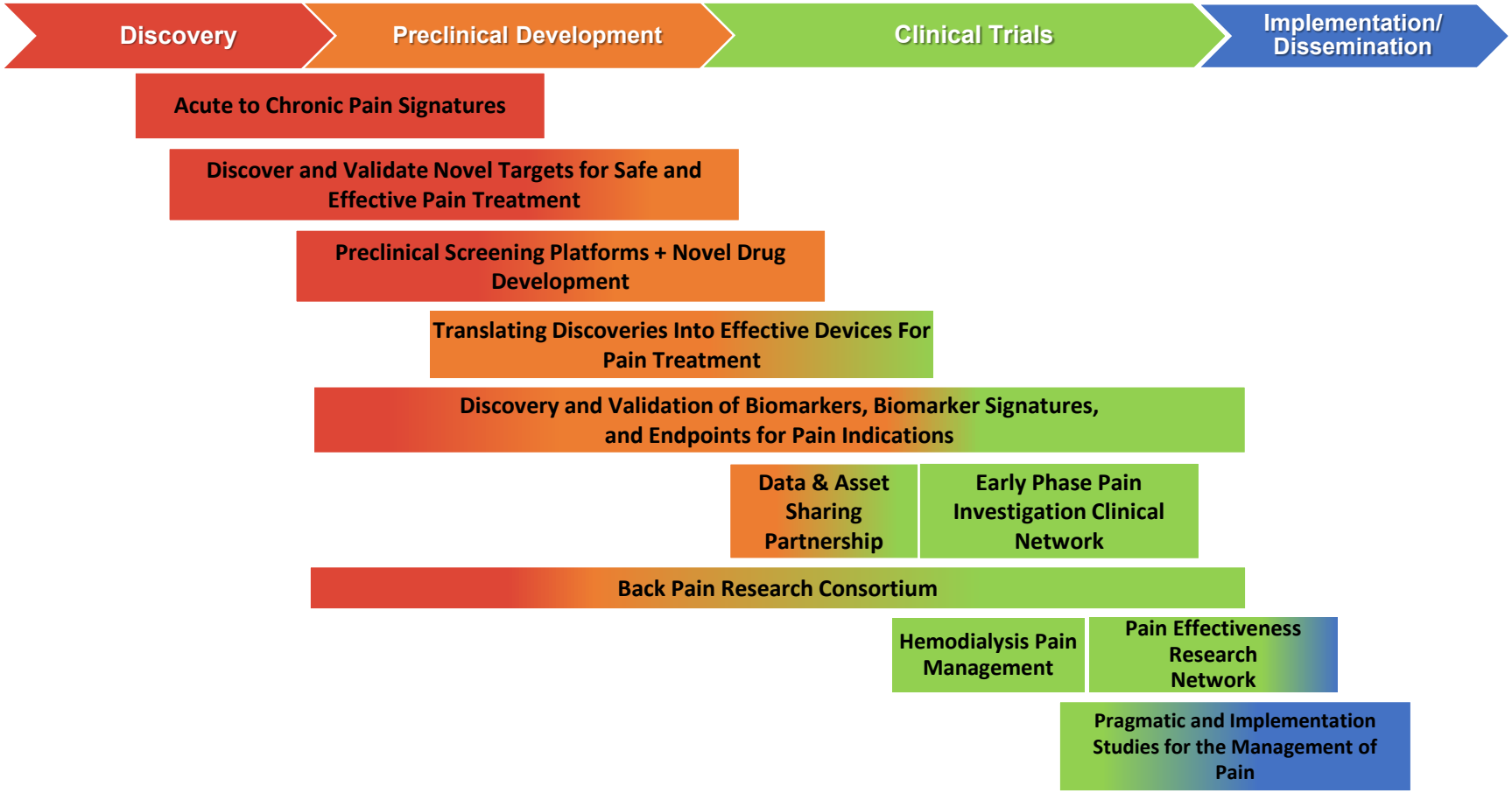
CLINICAL: Algorithms to match patients to best treatments based on phenotype and psychosocial context

NIH BACPAC Research Program

Pain Management Effectiveness and Implementation Research

- Pain Management ERN: To inform clinicians about the effectiveness of interventions or management strategies that will improve functional outcomes and reduce pain across the continuum of acute to chronic pain associated with many types of pain conditions
- Integrated care for hemodialysis patients: To develop tailored interventions for pain control and reduce reliance on opioids for hemodialysis patients
- Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing (PRISM): To integrate interventions with demonstrated efficacy into health care systems and implement health care system change toward evidence-based pain management

HEAL Programs for Pain Cover the Research Spectrum



Thank You!

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Discover and Validate Novel Targets for Safe and Effective Pain Treatment

Previously identified targets

Basic biology target discovery projects

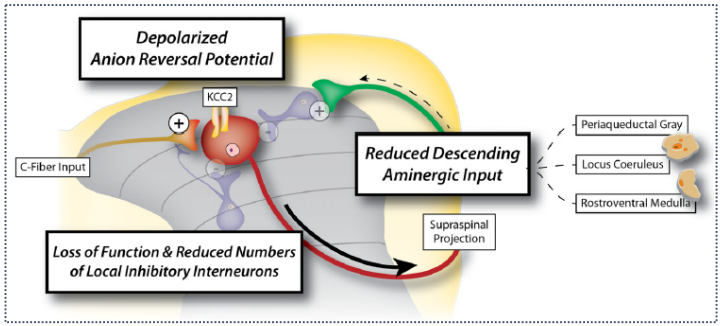
- Encourage collaboration from other fields
- Designed to reveal novel targets for small molecules, natural products, biologics, devices
- Devices: discovery of new sites for stimulation or electrophysiological signatures
- Open to all pain systems in CNS or periphery

Pain target validation

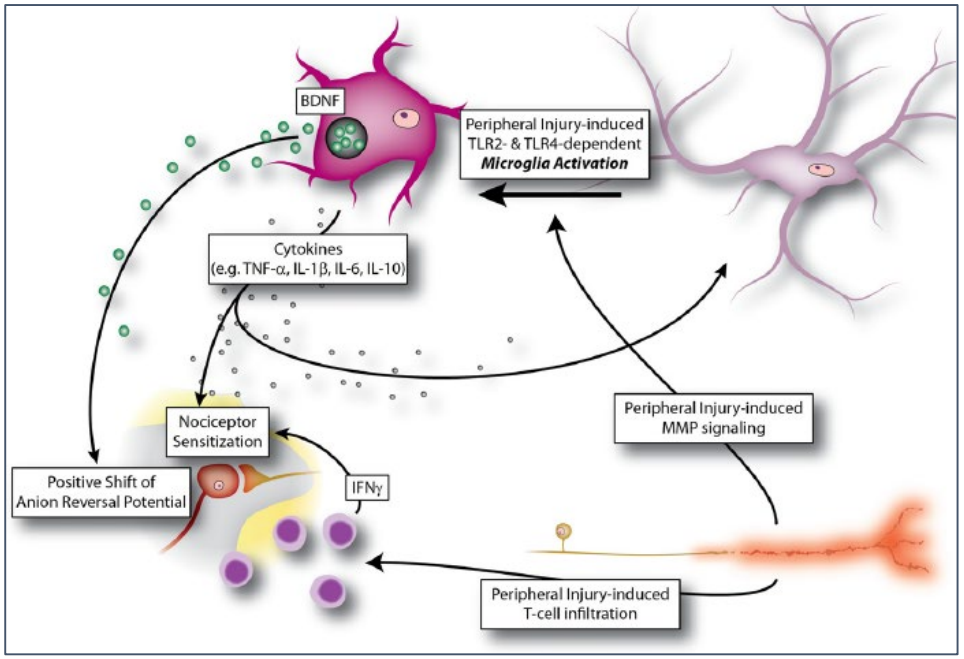
- Reproducibility and Robustness
  - Multi-site
  - Multiple strains/species
  - Sex
  - Age
- Generalizability of effect
  - Multiple pain models
- Test in animal model systems developed to better inform human studies
- Validation of pharmacodynamic and predictive biomarkers

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

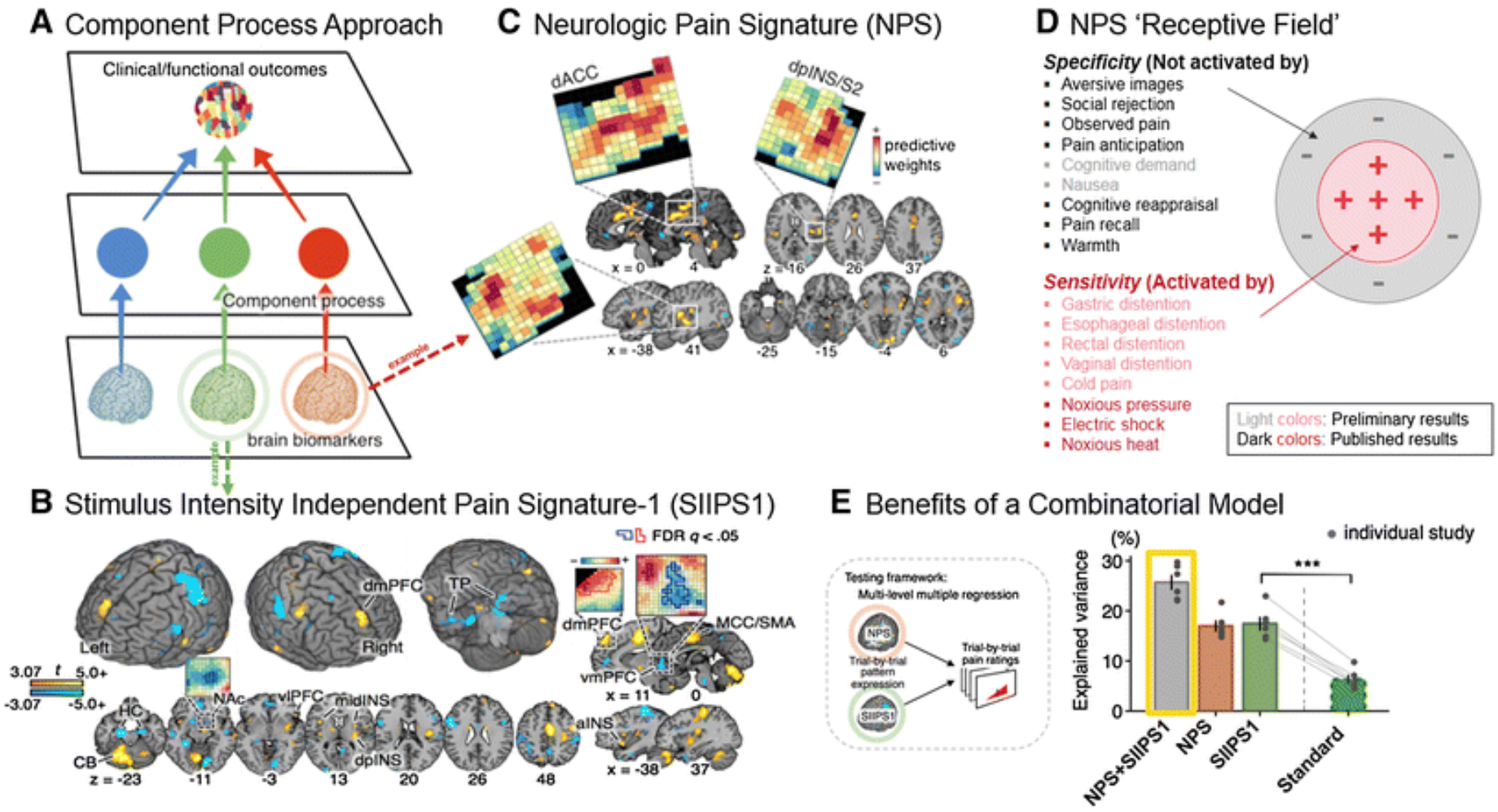
- To promote the basic science discovery and validation of **novel targets** for the treatment of pain that can be used to develop treatments that have minimal side effects and little to no abuse/addiction liability



Role of inflammatory cells and pathways in sensitization nerve and spinal cord.



Biomarkers: Modeling Pain Using fMRI



National Institutes of Health
Turning Discovery Into Health

Tor Wager: Neurosci Bull. 2018 Feb;34(1):208-215.

Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

To develop tailored interventions for pain control and reduce reliance on opioids for hemodialysis patients

Develop a multipronged and non-opioid approach to managing pain that uses precision treatment strategies based on individual needs

- Evaluate non-addictive analgesics to reduce pain
- Evaluate behavioral approaches for pain management
- Identify risk factors for opioid dependence
- Assess and treatment co-morbid conditions
- Enhance electronic health records to capture study outcome data

81% of hemodialysis patients suffer with pain, 62% received opioids, 23% high dose prescription. Headache, AV-fistula pain, musculoskeletal pain.

Pain Management Effectiveness Research Networks and Trials

To inform clinicians about the effectiveness of interventions or management strategies that will improve functional outcomes and reduce pain across the continuum of acute to chronic pain associated with many types of pain conditions

Evaluate the effectiveness of pharmacologic and nonpharmacologic therapies for a broad array of pain conditions

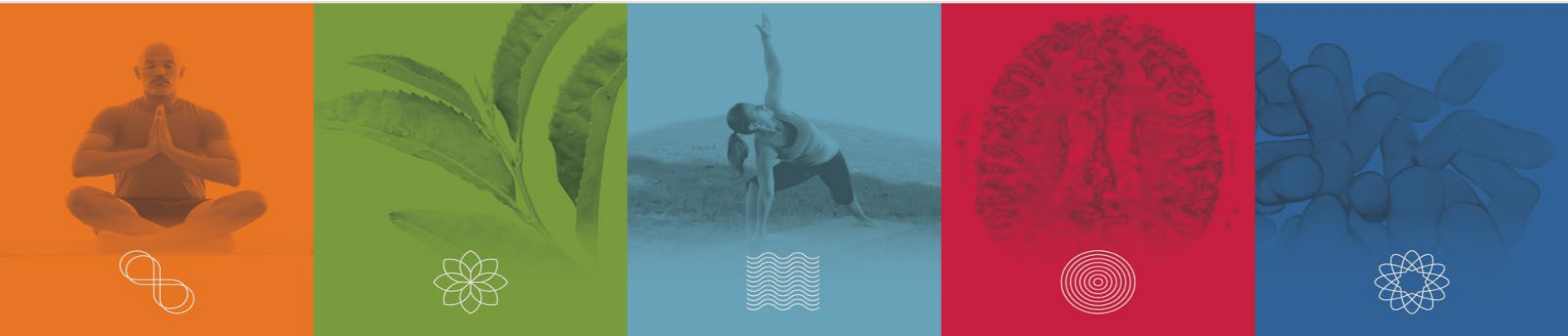
- Comparative Effectiveness Research Network: leverage NCATS' Trial Innovation Network
- Build pain expertise in coordinating centers and throughout CTSAs
- NIH will solicit proposals for Phase 3 clinical trials to inform best practices in pain management and minimize risk of addiction
- Coordinate data elements and storage with EPPIC-net and PRISM

Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing: PRISM

To integrate interventions with demonstrated efficacy into health care systems and implement health care system change toward evidence-based pain management

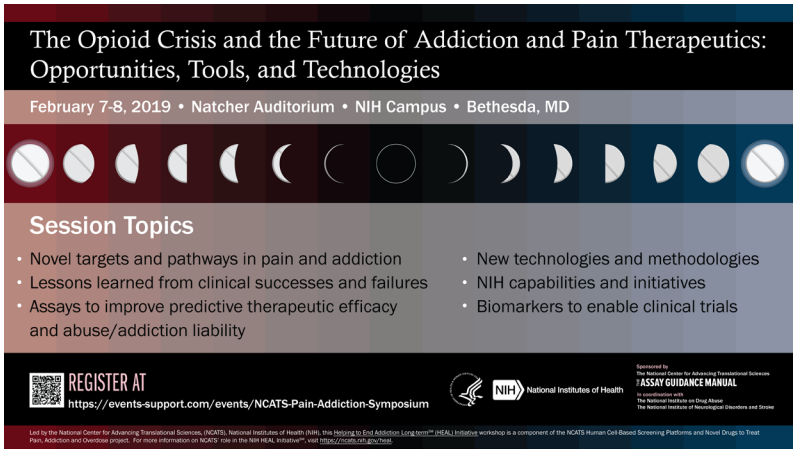
Conduct efficient, large-scale pragmatic trial or implementation science studies to improve pain management

- Embed the intervention under study into real world settings
- Collect data through the electronic records of the health care system
- Leverage the NIH Health Care Systems Collaboratory
- Focus on non-pharmacological approaches
- Collaboration with CMS for Medicare coverage consideration



Nov. 14-15, 2018

Discovery and Validation of Biomarkers to Develop Non-Addictive Therapeutics for Pain



Feb. 7-8, 2019

Scientific challenges and opportunities from bench to bedside

Jan. 30-31, 2019

State of the art in animal pain models and best practices

Feb. 6, 2019

Discovery and development opportunities for natural products