NIH · Helping to End Addiction Long-term

Introduction to the HEAL (Helping to End Addiction Long-term) Initiative

Francis S. Collins, MD, PhD

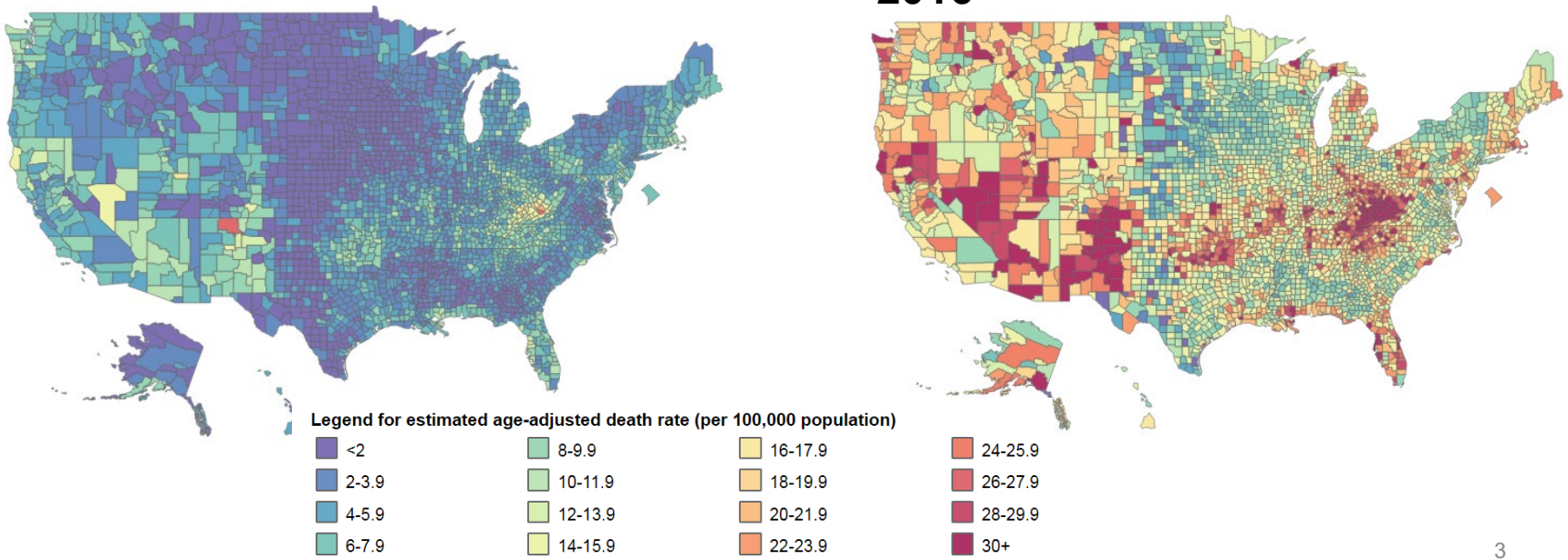
Director, National Institutes of Health

The Crisis: National Overdose Death Rates

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

1999

2016



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

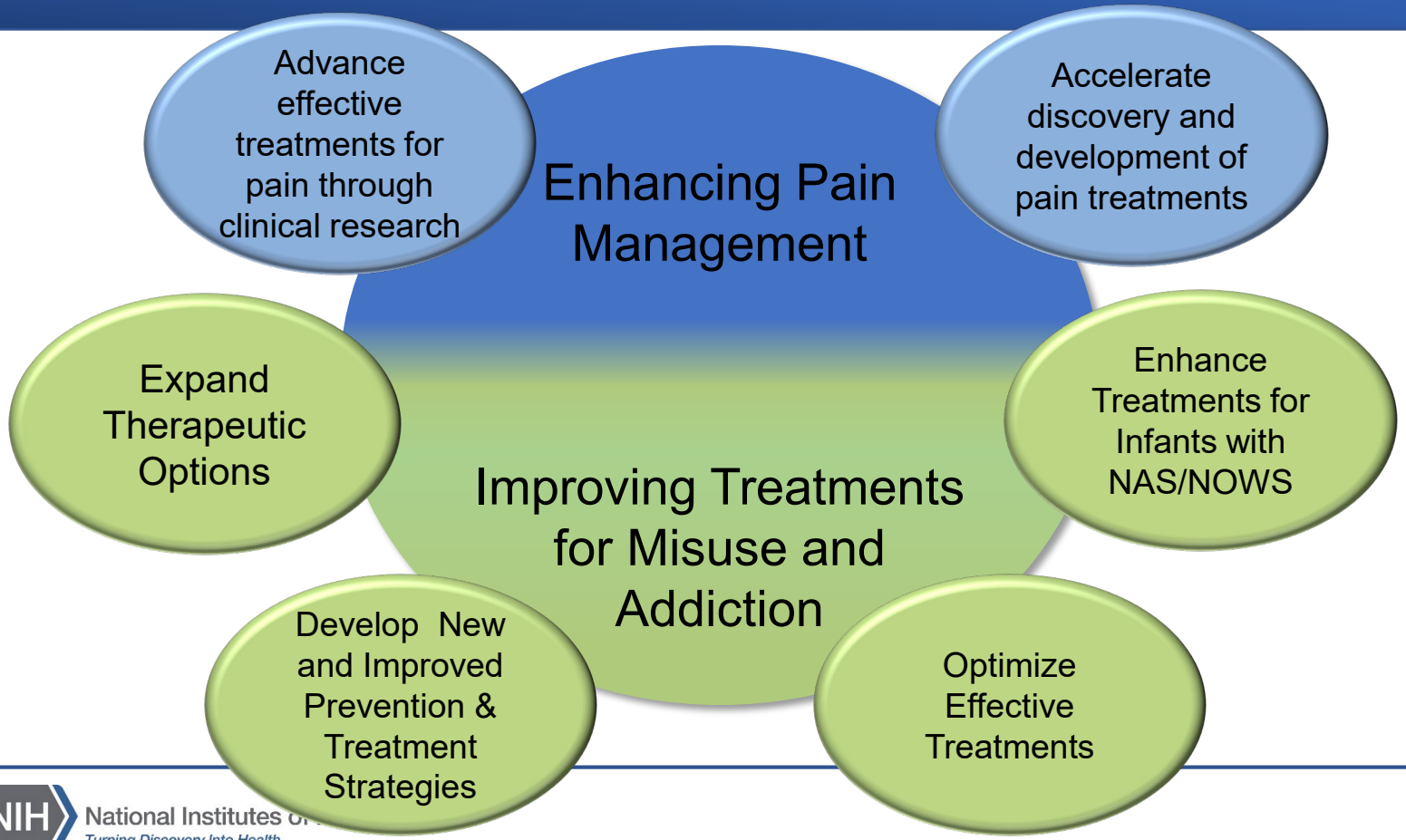
The Response:
Helping to End Addiction Long-term (HEAL) Initiative

- 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
  - 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

HEAL Initiative Research



Improving Prevention and Treatment Strategies for Opioid Addiction

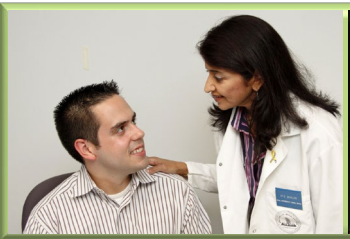
- Expand therapeutic options
  - New, more user-friendly formulations of existing medications
  - Longer duration, more powerful overdose-reversers
  - New approaches to reverse respiratory depression
  - Immunotherapies for opioids to prevent relapse and overdose
  - New targets and approaches for treating Opioid Use Disorder (OUD)

Improving Prevention and Treatment Strategies for Opioid Addiction

- Develop New and Improved Prevention & Treatment Strategies
  - Preventing at risk adolescents from transitioning to OUD as they transition to adulthood
  - Understanding the role of sleep dysfunction in OUD and recovery
  - Managing opioid misuse and low severity OUD
  - Determining the optimal length of medication treatment for OUD
  - Optimizing collaborative care for people with OUD and common mental disorders

Improving Prevention and Treatment Strategies for Opioid Addiction

- Optimize Effective Treatments
  - Enhancing the NIDA Clinical Trials Network to address opioids
  - Promoting innovation in the criminal justice system
    - Justice Community Opioid Intervention Network
  - Understanding the role of behavioral health interventions
    - Behavioral Research to Improve Adherence to Medication-based treatment for OUD (BRIM)
  - Integrating multiple evidence based interventions in communities
    - The HEALing Communities Study



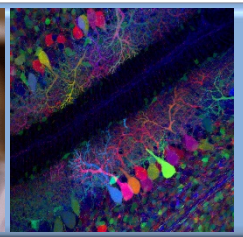
Improving Prevention and Treatment Strategies for Opioid Addiction

- Enhance Treatments for Infants with NAS/NOWS*
  - Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome
    - ACT NOW Study
  - Understanding the long-term consequences of early opioid exposure
    - HEALthy Brain and Cognitive Development (BCD) Study

*Neonatal Abstinence Syndrome/ Neonatal Opioid Withdrawal Syndrome (NOWS)

Enhancing Pain Management

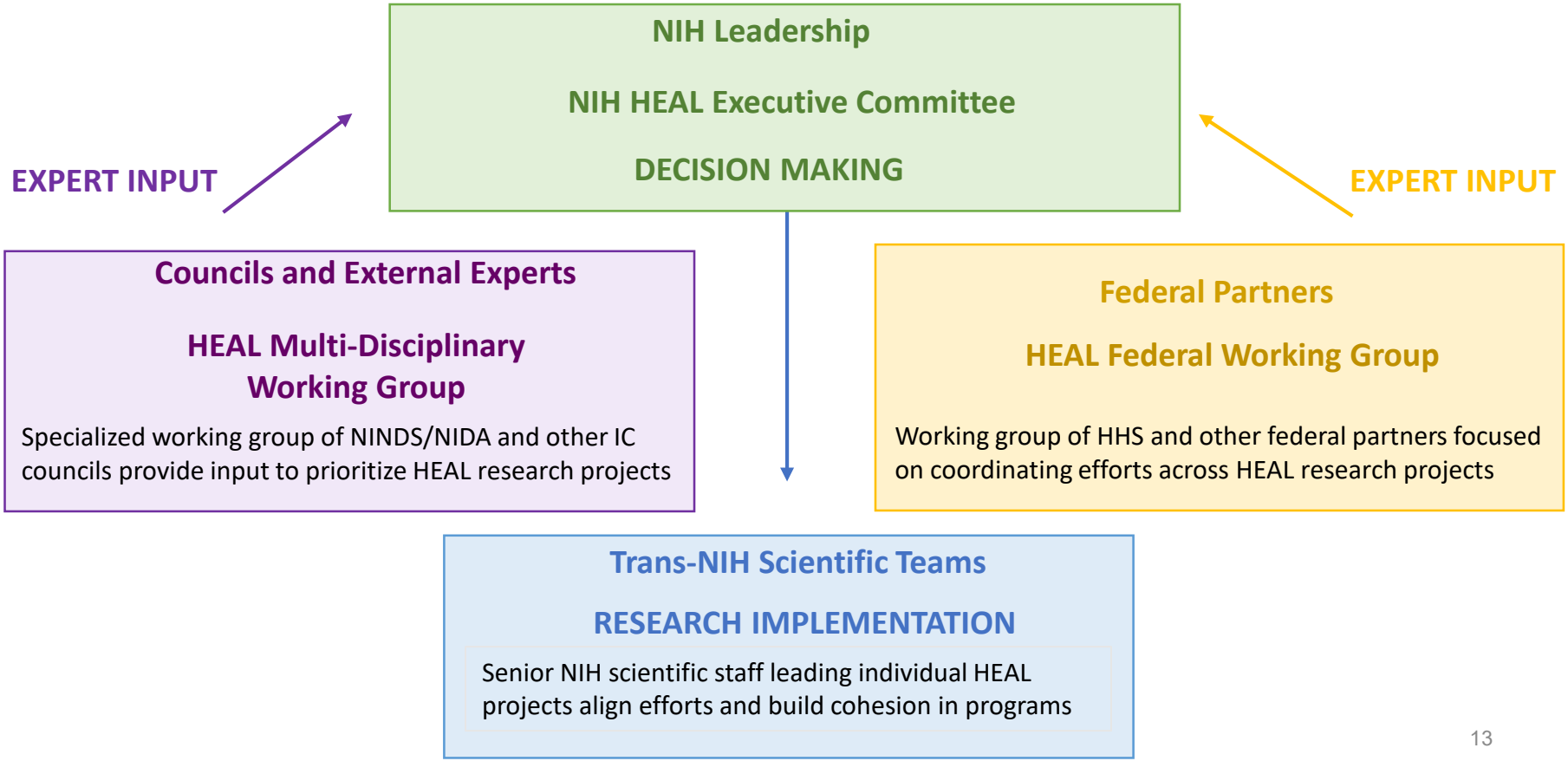
- Accelerate discovery and development of pain treatments
  - Understanding the origins of chronic pain
    - Acute to Chronic Pain Signatures Program
  - Discovery and validation of novel targets for safe and effective pain treatment
  - Engineering preclinical screening platforms + novel drug development
  - Translating discoveries into effective devices for pain treatment



Enhancing Pain Management

- Advance effective treatments for pain through clinical research
  - Test novel treatments in a new clinical trials network
    - Early Phase Pain Investigation Clinical Network (EPPIC Net)
    - Back Pain Research Consortium
  - Establish best strategies for management of acute and chronic pain
    - Pain Management Effectiveness Research Network (ERN)
    - Integrated approach to pain, opioid use in hemodialysis patients
    - Pragmatic and Implementation Studies for the Management of Pain (PRISM)

NIH Helping to End Addiction Long-term (HEAL) Initiative: Governance Overview



HEAL Initiative Governance: Multi-Disciplinary Working Group

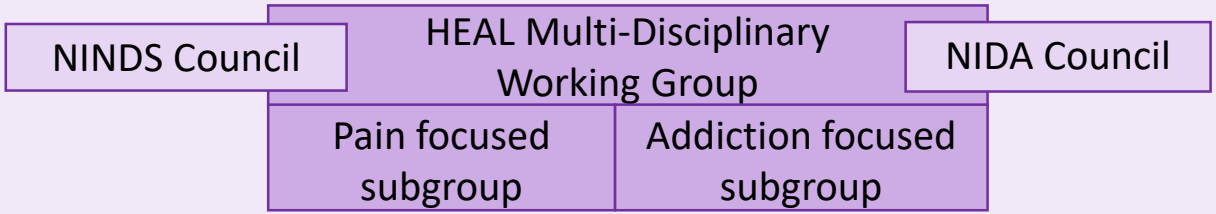
EXPERT INPUT

NIH HEAL Executive Committee

DECISION MAKING

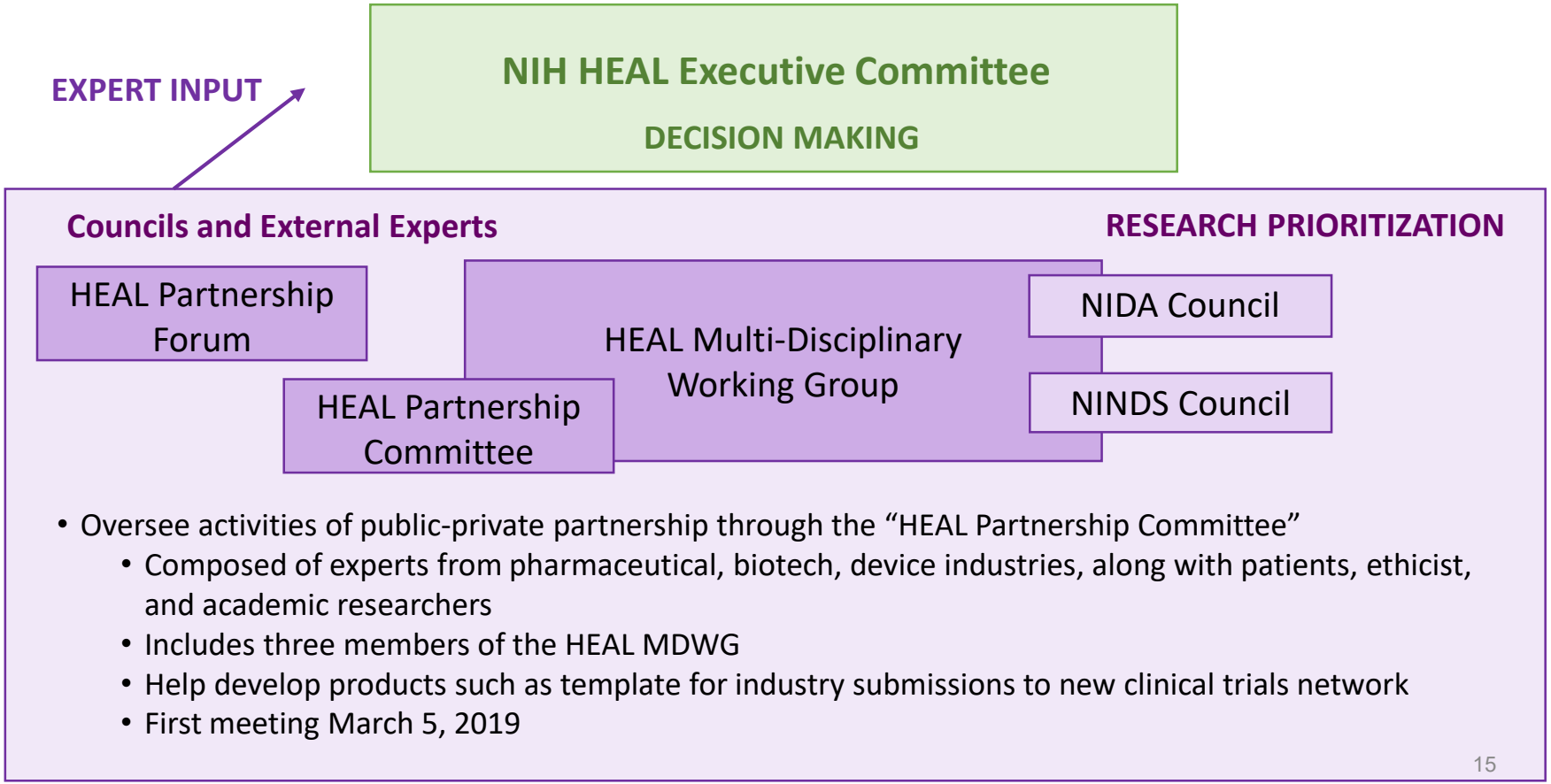
Councils and External Experts

RESEARCH PRIORITIZATION



- Specialized working group of NINDS, NIDA, other IC councils provide expert input on HEAL research
- 16 working group members – some council some ad hoc members
- Will not review every HEAL FOA or program
  - Some FOAs to go directly to relevant IC council – determined by Executive Committee
- Provides input on state of the science in HEAL research areas and different pain conditions
  - Health services research, multi-disciplinary research and emerging opportunities

HEAL Initiative Governance: Multi-Disciplinary Working Group



- Oversee activities of public-private partnership through the "HEAL Partnership Committee"
  - Composed of experts from pharmaceutical, biotech, device industries, along with patients, ethicist, and academic researchers
  - Includes three members of the HEAL MDWG
  - Help develop products such as template for industry submissions to new clinical trials network
  - First meeting March 5, 2019

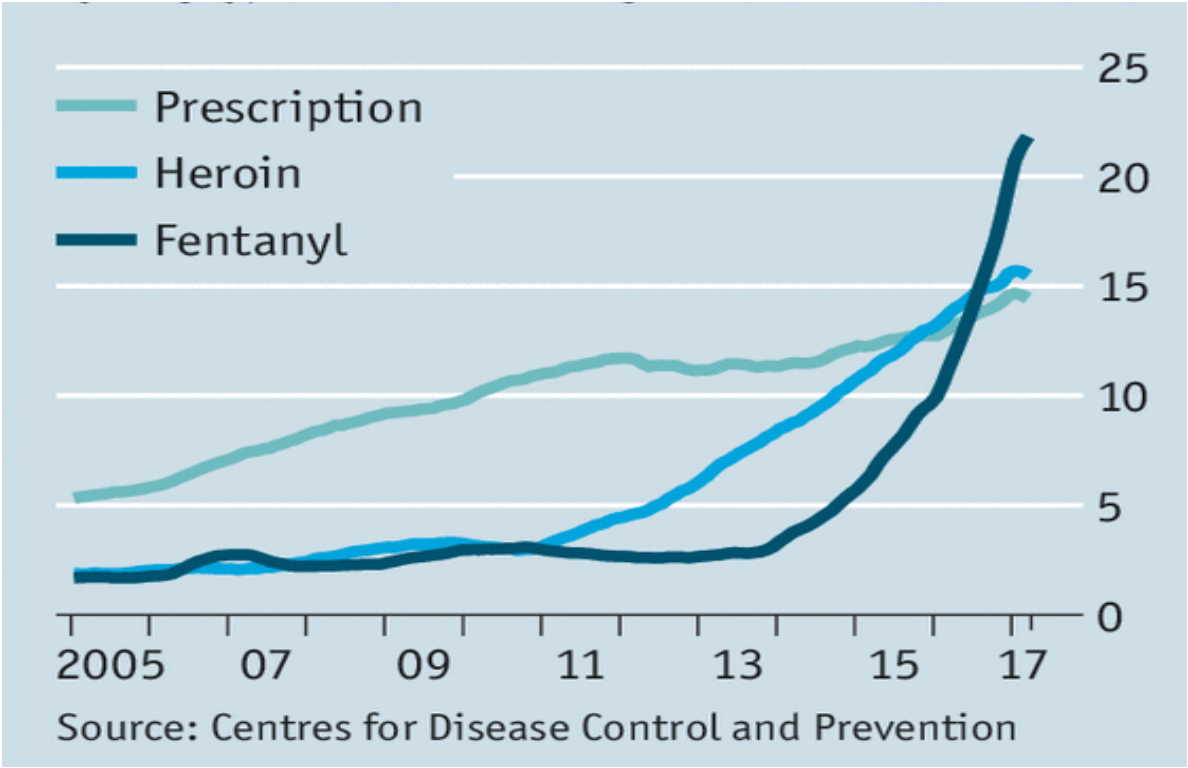
Improving Prevention and Treatment Strategies for Opioid Misuse and Addiction Through HEAL

Nora D. Volkow, MD

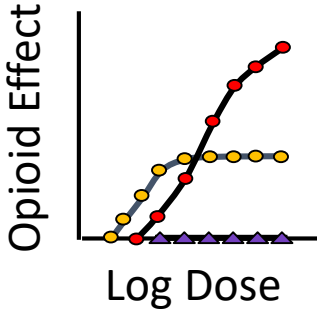
Director

National Institute on Drug Abuse

Evolution of the Opioid Crisis: Overdose Fatalities



Medication Assisted Treatment (MAT)



Full Agonist
(Methadone: Daily Dosing)

Partial Agonist
(Buprenorphine: 3-4X week)

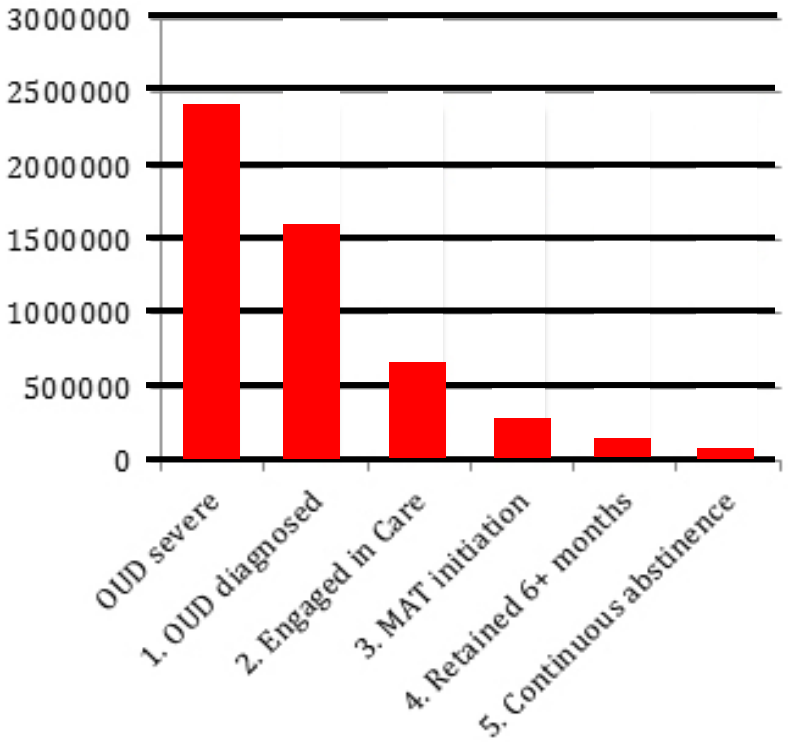
Antagonist
(Naltrexone: ER 1 month)

DECREASES:
- **Opioid use**
- **Opioid-related overdose deaths**
- **Criminal activity**
- **Infectious disease transmission**

INCREASES
- **Social functioning**
- **Retention in treatment**

MAT is highly underutilized!
Relapse rates are very high (50% in 6 months)

OUD Cascade of Care in USA



Williams AR, Nunes E, Olfson M. Health Affairs Blog, 2017.

Improving Prevention and Treatment for Opioid Misuse, Addiction and Overdose

Priority Research Areas:

Expand Therapeutic Options	*Optimize Effective Treatment Strategies*	*Develop New/Improved Prevention & Treatment Strategies*	*Enhance Treatments for Infants with NAS/NOWS*

Research Opportunities:

• New formulations • Longer duration • Respiratory depression • Immunotherapy • New targets and approaches	• Clinical trials expansion • Criminal justice innovation • Collaborative care • Behavioral interventions • Multi-site implementation	• Treatment of early/moderate OUD • Optimal length of medication treatment • Prevention in transition to adulthood	• Brain development of opioid-exposed infants • ACT NOW

Expand Therapeutic Options: OUD and OD Reversal

- New Formulations for MOUD that facilitate compliance
- New Medication Targets for OUD
- Drug combinations to improve retention (lofexidine + buprenorphine)
- Stronger, longer acting opioid antagonists and new targets to address Overdoses (OD) from synthetic opioids (e.g. fentanyl) and drug combinations (bdz + opioids)
- Stimulation devices to prevent respiratory depression
- OD, alert technologies, and naloxone autoinjectors
- Post-overdose interventions to ensure engagement in treatment

New Medications: RFA DA-19-002: Rolling acceptance of applications

Optimize Effective Treatment Strategies: Clinical Trials Network Expansion Project

- Focused studies on opioid addiction
  - Optimizing Retention, Duration and Discontinuation Strategies for OUD medications (MOUD) in healthcare
  - Strategies for inducting OUD medications in hospitalized patients and enhancing post-discharge care
  - Extended-release medications
  - Implement ED-initiated and compare formulations of buprenoprhine
- Rural expansion of OUD medication treatment using telemedicine and mHealth approaches
- More effective models for linkage to care
- Opioid registry in diverse health care delivery systems

RFA-DA-19-008: Awards for 4 new nodes in Summer 2019

Optimize Effective Treatment Strategies: Justice and Community Opioid Network (JCOIN)

- Opioid Innovation in the Criminal Justice System
  - Justice Community Opioid Innovation Network (JCOIN)
  - Generate real-world evidence to address needs of individuals with OUD in justice-settings
- Progress to Date:
  - 11 supplement awards made in September 2018
  - Solicitations released December, 2018 for Research Centers, Coordination and Translation Center, and Methodology and Analytics Center
  - Expected awards total $30M, Awards expected Early Fall 2019

Optimize Effective Treatment Strategies: The HEALing Communities Study

- Develop and test strategies to help communities respond to opioid crisis with a focus on achieving a 40% reduction in 3 years for OD fatalities
- Measure impact of integrating evidence-based prevention and treatment for opioid misuse, OUD, OD, and fatalities across multiple settings (healthcare, behavioral health, justice, communities.)
- Determine factors (structural, organizational, policy, etc.) that contribute to successful implementation and sustainability of the integrated interventions
- Determine cost-effectiveness of integrated intervention compared to standard of care
- Awards Expected: April 2019

Develop New/Improved Prevention and Treatment Strategies

- Prevention in the Transition to Adulthood
  - Studies to prevent OUD in older adolescents and young adults
- Sleep Dysfunction
  - Sleep and circadian factors relevant to addiction
- Management of Subsyndromal and Low-severity OUD
  - Identify and treat patients in general medical settings with co-occurring pain/mental health disorders
- Optimal Length of Medication Treatment
  - Trial will focus on buprenorphine and naltrexone
- Collaborative Care Model
  - Adapted to patients with OUD and mental health conditions

William Casey

Improve Outcomes for Infants with Neonatal Abstinence Syndrome and Opioid Affected Families

- Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW)
  - Innovative ways to identify and treat newborns exposed to opioids
- HEALthy Brain and Child Development Study:
  - Large multi-site longitudinal study to examine brain, cognitive, behavioral, social, and emotional development beginning prenatally and extending through childhood.
  - Oversample for prenatal opioid exposure
- Progress to Date:
  - R34 Planning Grant Funding Opportunity Announcements RFA-DA-19-029; RFA-DA-19-036
    - Applications due: March 25, 2019;
    - Awards expected: September 2019

Enhancing Pain Management through HEAL

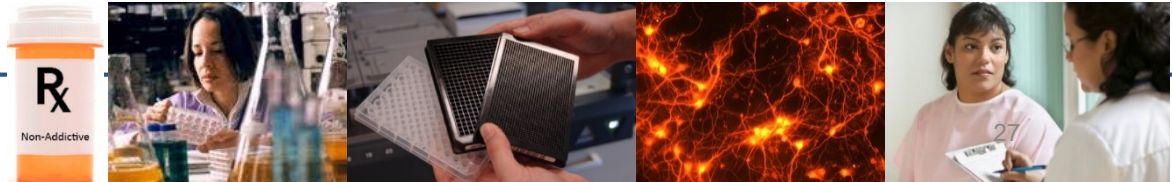
Walter J. Koroshetz, MD
Director
National Institute of Neurological Disorders and Stroke

Priorities in Research to Enhance 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:

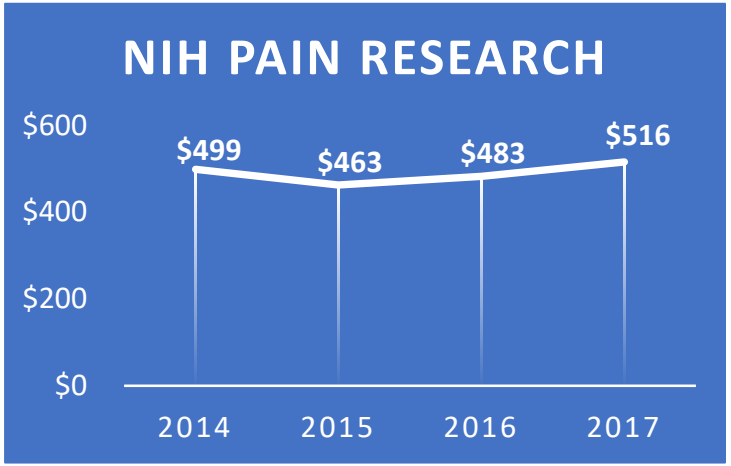
www.nih.gov/heal-initiative



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



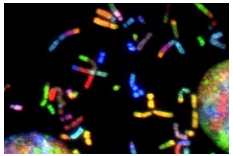
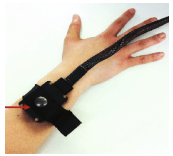
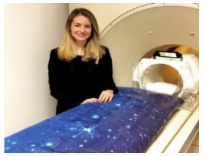
The NIH Pain Consortium was established with the goal of enhancing pain research and promoting collaboration across NIH

Understand the biological underpinnings of chronic pain

Acute to Chronic Pain Signatures

- Objective biosignatures to identify susceptibility or resilience to chronic pain
  - Phenotyping
  - Genotyping
  - Sensory tests
  - Imaging
  - -omics
- Outcomes
  - Mechanisms
  - Novel therapeutic targets
  - Cohort stratification
  - Prevention



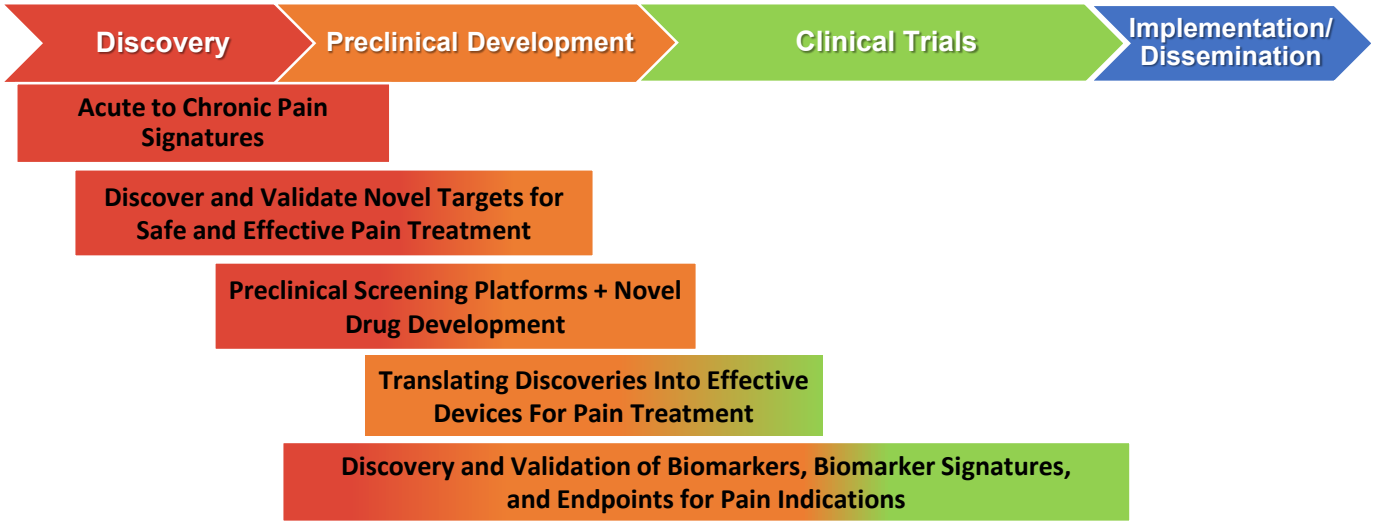





Structure:
- Clinical Coordination Center
- Clinical Centers
- Omics Data Generation Centers
- Data Integration and Resource Center

Awards expected in Spring 2019

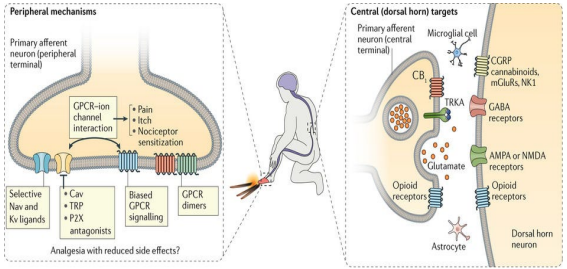
https:/comm/onfund.nih.gov/pain

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 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
NOT-NS-18-073 – Administrative Supplements

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

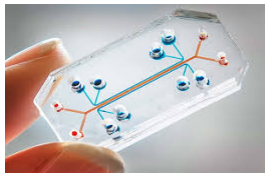
Previously identified targets

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

More info coming later today!

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



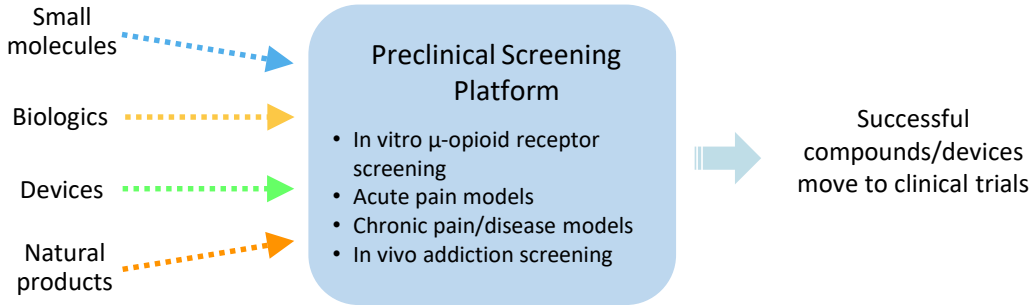
- Support preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapies to treat pain.
- Develop human cell/tissue models
  - Peripheral and central nervous system
  - Normal and disease states
  - iPSC-derived neurons, 3D printed organoids, tissue 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)

More info coming later today!

Preclinical Screening Platform for Pain (PSPP)

- Will 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



https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative-PSPP

More info coming later today!

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
- 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

Brain Research through Advancing Innovative Neurotechnologies

Stimulating Peripheral Activity to Relieve Conditions

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

Analytical and/or Clinical Validation of a Candidate Biomarker for Pain: Facilitate the discovery and development of high-quality biomarkers to accelerate the development of non-addictive therapeutics for the treatment of pain conditions

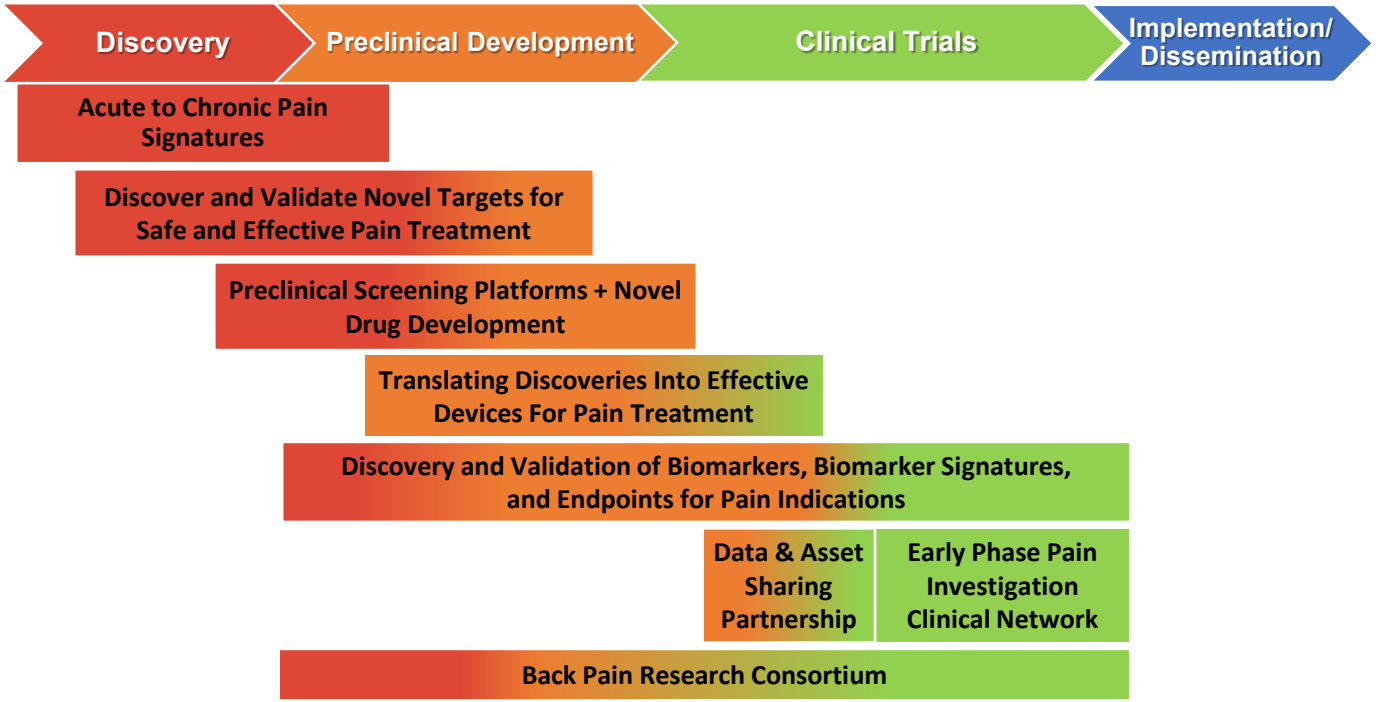
RFA-NS-18-046 – R61/R33

Discovery of Biomarkers, Biomarker Signatures, and Endpoints for Pain: Goal is to 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

RFA-NS-18-041 – R61/R33

Goal is to facilitate the discovery of robust biomarkers, biomarker signatures and objective endpoints for pain conditions

Advance new non-addictive pain treatments through the clinical pipeline



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!

Back Pain Research Consortium: BACPAC

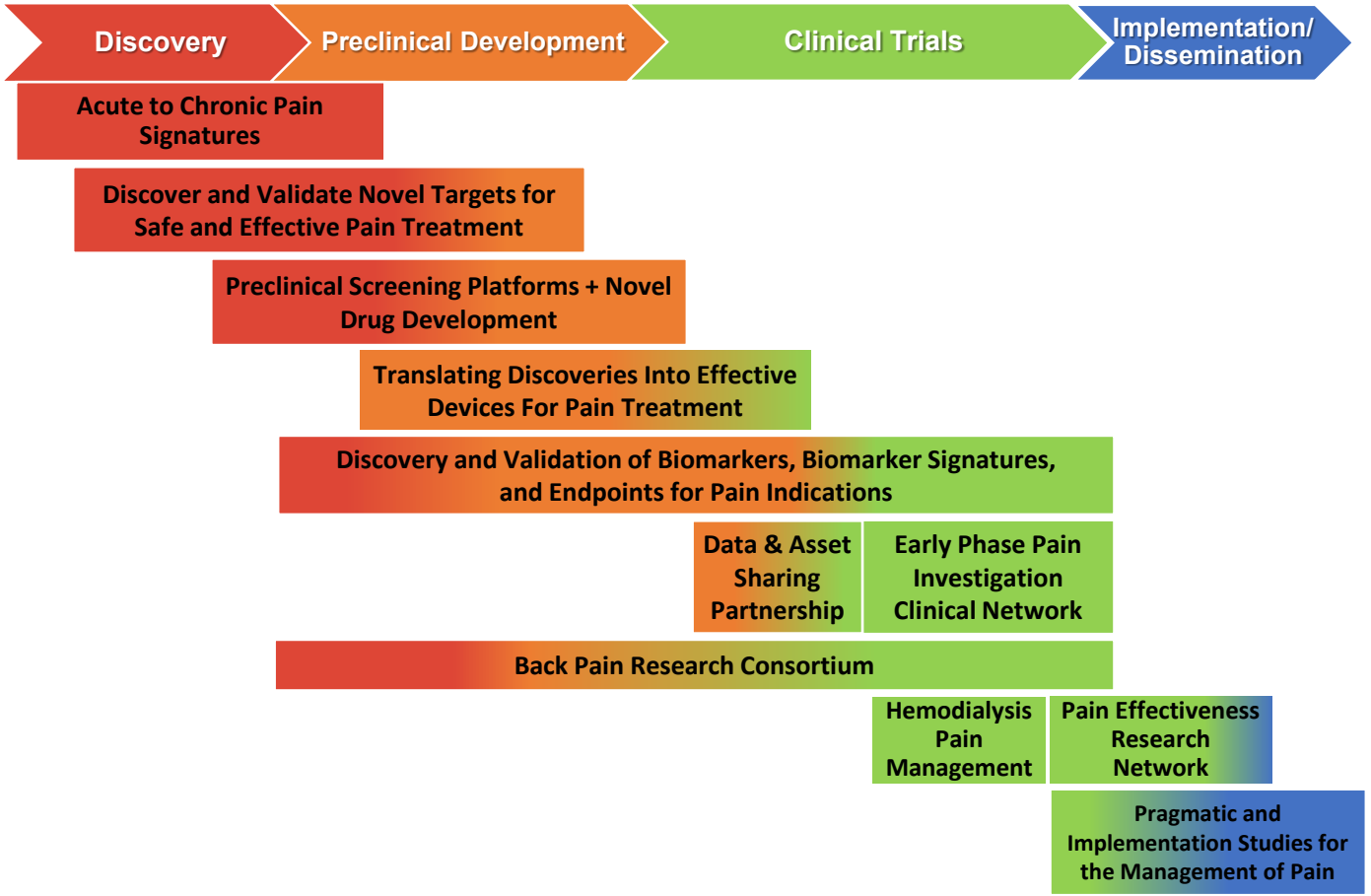
Back Pain Consortium (BACPAC) Research Priorities
A patient-centric, translational research program

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

Establish the best pain management strategies for acute and chronic pain conditions



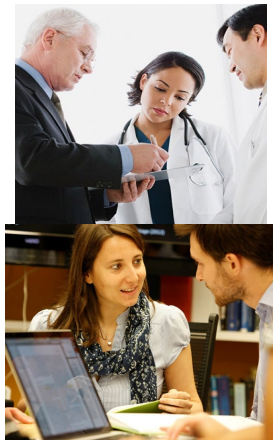
Pain Management Effectiveness Research Networks and Trials

- ***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
  - Pain expertise in coordinating centers
  - 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

More info coming later today!

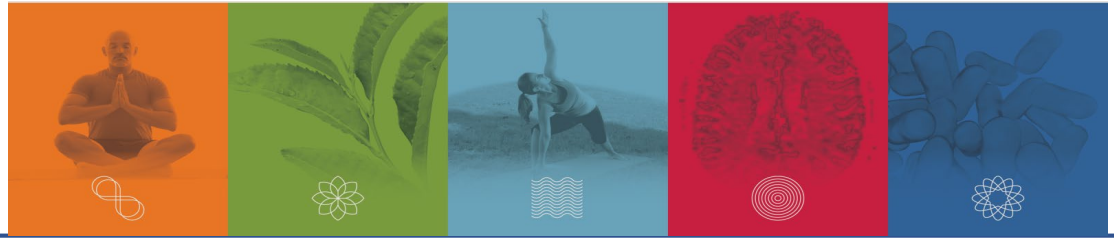
Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

- 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

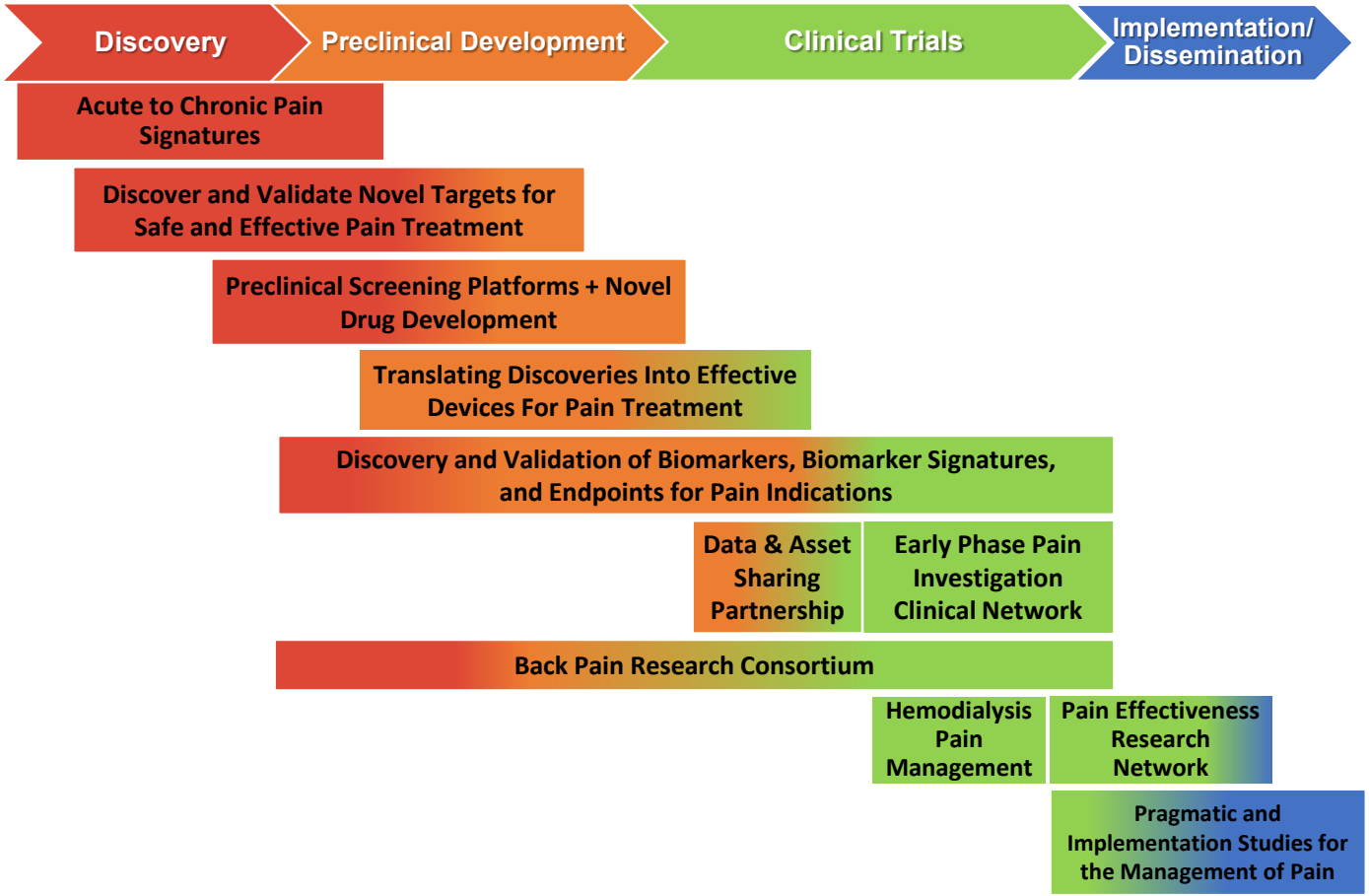


Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing: PRISM

- **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



HEAL Programs for Pain Cover the Research Spectrum



Questions/Discussion