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)

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

www.nih.gov/heal-initiative
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

Enhancing Pain Management

- Advance effective treatments for pain through clinical research
- Accelerate discovery and development of pain treatments
- Expand Therapeutic Options
- Develop New and Improved Prevention & Treatment Strategies
- Optimize Effective Treatments
- Enhance Treatments for Infants with NAS/NOWS

Improving Treatments for Misuse and Addiction

NIH - National Institutes of Health
Turning Discovery Into Health
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)
Federal Partners

Working group of HHS and other federal partners focused on coordinating efforts across HEAL research projects

NIH Leadership

NIH HEAL Executive Committee

NIH HEAL Multi-Disciplinary Working Group

Specialized working group of NINDS/NIDA and other IC councils provide input to prioritize HEAL research projects

Councils and External Experts

Federal Partners

HEAL Federal Working Group

Working group of HHS and other federal partners focused on coordinating efforts across HEAL research projects

Trans-NIH Scientific Teams

RESEARCH IMPLEMENTATION

Senior NIH scientific staff leading individual HEAL projects align efforts and build cohesion in programs
NIH HEAL Executive Committee

DECISION MAKING

Councils and External Experts

NINDS Council

HEAL Multi-Disciplinary Working Group

NIDA Council

Pain focused subgroup

Addiction focused subgroup

EXPERT INPUT

• 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

RESEARCH PRIORITIZATION
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
Conflict of Interest Reminder and Declarations

Lawrence Tabak DDS, PhD
Principal Deputy Director, NIH
Deputy Ethics Counselor, NIH
Without tension
There can be no music
Role of NIH Working Groups

• To serve as fact-finding bodies to gather information, conduct research, analyze relevant issues and/or draft proposed position papers

• To deliver recommendations for deliberation by the full Federal Advisory Committee(s)
Working Group Composition

- Working Groups (WGs) are comprised of two types of members:
  - Special Government Employees (SGEs) - Serving on an NIH Federal advisory committee and as a member of the MDWG
    - Will continue to be covered by Conflict of Interest statutes and regulations
    - Are required to file Confidential Financial Disclosure Report (OGE Form 450) and subsequent quarterly updates
    - Follow Designated Federal Official’s (DFO’s) directions re: recusal obligations
• Working Groups (WGs) are comprised of two types of members (cont):
  • Non-SGEs - Selected for specific expertise as it relates to the needs of the working group
    • Are not held to the same Government Ethics rules and regulations as SGEs
    • Are required to complete the certification process as managed by the DFO
Potential Sources of Bias

• The following interests and relationships are potential sources of bias for a Working Group member or his/her immediate family member, among others:

• Holds a financial, equity, or a patent or other proprietary interest in an organization whose product or product concept:
  • is a subject of and/or competes with a product or product concept that is the subject of deliberations
  • would uniquely benefit from research emphasis in a defined area
Potential Sources of Bias (cont)

• The following interests and relationships are potential sources of bias for a Working Group member or his/her immediate family member, among others

• Seeks employment in an organization or serves as an officer, director, trustee, partner, or employee of an organization whose product or product concept is a subject of and/or competes with a product or product concept to be discussed
How to Identify and Resolve a Conflict

• SGEs
  • Please excuse yourself from discussions of specific matters that could affect interests and relationships identified on your recusal list
  • Please complete the certification process as managed by the DFO
How to Identify and Resolve a Conflict (cont)

• Non-SGEs
  • Please read the Conflict of Interest and Confidentiality Information for Working Group Participants and review the WG charge and meeting agenda
  • Please read the Certification Statement and certify whether you have a potential or actual conflict of interest (COI) with an agenda item for each meeting
  • Please disclose the COI to the DFO and working group prior to any discussions of that item so it can be reflected in the minutes along with the group’s determination of how to handle the conflict
Material made available to the working group, as well as discussions during closed meetings, are strictly confidential and may not be disclosed or discussed with anyone who has not been officially designated to participate in the working group meeting.

Participants must certify that they will maintain the confidentiality of the meeting materials and discussions and not disclose this information to any other individual, except as authorized by the NIH advisory committee to which the group reports.
Improving Prevention and Treatment Strategies for Opioid Misuse and Addiction Through HEAL

Nora D. Volkow, MD
Director
National Institute on Drug Abuse
### Improving Prevention and Treatment for Opioid Misuse, Addiction and Overdose

#### Priority Research Areas:

<table>
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<tr>
<th>Expand Therapeutic Options</th>
<th>Optimize Effective Treatment Strategies</th>
<th>Develop New/Improved Prevention &amp; Treatment Strategies</th>
<th>Enhance Treatments for Infants with NAS/NOWS</th>
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#### Research Opportunities:

- **Expand Therapeutic Options**
  - New formulations
  - Longer duration
  - Respiratory depression
  - Immunotherapy
  - New targets and approaches

- **Optimize Effective Treatment Strategies**
  - Clinical trials expansion
  - Criminal justice innovation
  - Collaborative care
  - Behavioral interventions
  - Multi-site implementation

- **Develop New/Improved Prevention & Treatment Strategies**
  - Treatment of early/moderate OUD
  - Optimal length of medication treatment
  - Prevention in transition to adulthood

- **Enhance Treatments for Infants with NAS/NOWS**
  - Brain development of opioid-exposed infants
  - ACT NOW
Expand Therapeutic Options: OUD and Overdose Reversal

- New Targets for OUD
- Drug combinations to improve retention (lofexidine + buprenorphine)
- Stronger, longer acting formulations and new targets for 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 Medication Outcomes: Craving, Insomnia, Depression
  - RFA DA-19-002: Rolling acceptance of applications
Research Priority: Develop New/Improved Prevention and Treatment Strategies

- 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
  - Randomized clinical trial of buprenorphine and methadone

- Collaborative Care Model
  - Adapted to patients with OUD and mental health conditions
Addiction Prevention and Treatment: Preventing OUD in Older Adolescents and Young Adults (ages 16 -30)

• Goal: Develop the evidence base for interventions and strategies to prevent initiation of opioid misuse and development of OUD in at-risk older adolescents and young adults

• Focus: Healthcare, justice and other systems and settings opportune for accessing and engaging at risk adolescents and young adults

• Components: HEAL Prevention Cooperative - up to 10 research projects and 1 coordinating center.
  • Two FOAs published:
    • UG3/UH3 Research Projects (RFA-DA-19-035)
    • U24 Coordinating Center (RFA-DA-19-034)
  • Applications due - 3/2019; Award Date - Fall 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: 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 buprenorphine
- 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: 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 OD 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
Enhance Treatments for Infants with Neonatal Abstinence Syndrome/Opioid Withdrawal Syndrome

• 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
HEAL Research to Enhance Pain Management

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
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

- **Discovery**
  - Acute to Chronic Pain Signatures
- **Preclinical Development**
  - Discover and Validate Novel Targets for Safe and Effective Pain Treatment
  - Preclinical Screening Platforms + Novel Drug Development
- **Clinical Trials**
  - Translating Discoveries Into Effective Devices For Pain Treatment
- **Implementation/Dissemination**
  - Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
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

![Diagram of pain pathways]

**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

**Previously identified targets**

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

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

Small molecules → Preclinical Screening Platform → Successful compounds/devices move to clinical trials

Biologics

Devices

Natural products

- In vitro µ-opioid receptor screening
- Acute pain models
- Chronic pain/disease models
- In vivo addiction screening

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
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

NIH National Institutes of Health
Turning Discovery Into Health
Advance new non-addictive pain treatments through the clinical pipeline

Discovery
- Acute to Chronic Pain Signatures
- Discover and Validate Novel Targets for Safe and Effective Pain Treatment
- Preclinical Screening Platforms + Novel Drug Development

Preclinical Development
- Translating Discoveries Into Effective Devices For Pain Treatment

Clinical Trials
- Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
- Data & Asset Sharing Partnership
- Early Phase Pain Investigation Clinical Network

Implementation/Dissemination
- Back Pain Research Consortium

NIH
National Institutes of Health
Turning Discovery Into Health
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

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

- **Discovery**
  - Acute to Chronic Pain Signatures
  - Discover and Validate Novel Targets for Safe and Effective Pain Treatment
  - Preclinical Screening Platforms + Novel Drug Development
  - Translating Discoveries Into Effective Devices For Pain Treatment
  - Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications

- **Preclinical Development**
  - Data & Asset Sharing Partnership
  - Early Phase Pain Investigation Clinical Network

- **Clinical Trials**
  - Back Pain Research Consortium
  - Hemodialysis Pain Management
  - Pain Effectiveness Research Network
  - Pragmatic and Implementation Studies for the Management of Pain

- **Implementation/Dissemination**
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

Discovery
- Acute to Chronic Pain Signatures
- Discover and Validate Novel Targets for Safe and Effective Pain Treatment
- Preclinical Screening Platforms + Novel Drug Development
- Translating Discoveries Into Effective Devices For Pain Treatment
- Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
- Data & Asset Sharing Partnership
- Early Phase Pain Investigation Clinical Network
- Back Pain Research Consortium
- Hemodialysis Pain Management
- Pain Effectiveness Research Network
- Pragmatic and Implementation Studies for the Management of Pain

Preclinical Development

Clinical Trials

Implementation/Dissemination
Questions/Discussion