NIH HEAL (Helping to End Addiction Long-termSM) Initiative Multi-Disciplinary Working Group

August 21, 2019
Wilson Hall, NIH Campus
Bethesda MD
Session 1: Overview and NIH HEAL Initiative
Activities Underway

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
Enhancing Pain Management

Improving Treatments for Misuse and Addiction

Pre-Clinical Research in Pain Management

Clinical Research in Pain Management

Expand Therapeutic Options

Enhance Treatments for Affected Newborns

Develop New/Improved Prevention & Treatment Strategies

Optimize Effective Treatments

Optimize Effective Treatments
Introduction to Agenda

Rebecca Baker, Ph.D.
Director, HEAL Initiative, Office of the Director
The Justice Community Opioid Innovation Network (JCOIN)

HEAL Multidisciplinary Working Group
August 21, 2019

Tisha Wiley, Ph.D.
Associate Director for Justice Systems
Chief, Services Research Branch
National Institute on Drug Abuse
HEAL Initiative Research Overview

- Enhancing Pain Management
- Improving Treatments for Misuse and Addiction
- Expand Therapeutic Options
- Develop New/Improved Prevention & Treatment Strategies
- Optimize Effective Treatments
- Enhance Treatments for Affected Newborns
- Pre-Clinical Research in Pain Management
- Clinical Research in Pain Management
Optimize Effective Treatments:

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

Missed Opportunities to Improve Public Health & Public Safety

- >10M arrested & 2M incarcerated annually
- 17-19% of inmates have used opioids; <1% receive MOUD
- <5% of jails offer MOUD to inmates
- 13x risk of dying of a drug overdose during re-entry
- MOUD during incarceration cuts mortality by up to 75%

- 95% return to community; 4.7M on probation or parole
- Justice-referred patients are ~1/10 as likely to receive MOUD
- Many drug courts or probation officers prohibit MOUD
JCOIN Vision & Priority Goals

**Vision**

*Every individual* involved in the justice system with a substance use disorder should have **access to effective treatment**, both while detained and upon return to the community.

**Priority Goals**

- Generate **new evidence** about what works and how to effectively implement
- Become a **go-to resource** for researchers and practitioners
- Develop a **network of researchers collaborating with practitioners** across justice and community-based service settings.
- **Build capacity** to conduct and apply research in justice settings
- Speed **science-to-practice translation** and feedback loops.
JCOIN Structure Overview

**Accelerator Supplements**
FY18/19 Only ($5.5M)
- Rapid Studies
- Baseline Data Collection: National Surveys
- Early Infrastructure

**Research Hubs**
UG1 ($23M/Y)
- Multi-site Studies
  - Each = Large Scale Project in 5+ Communities
  - Cascade of Care Focus
  - Each has Justice & Treatment Partner

**Supportive Infrastructure**
- Coordination and Translation Center CTC U2C ($3.5M/Y)
  - Implementation Science & Translational Outreach

**Methodology and Advanced Analytics Resource Center MAARC U2C ($3.5M/Y)**
- Data Infrastructure

**Novel Studies**
- 12 Projects Funded
  - Sept. 2018 – May 2019
- 10 Projects Funded
  - July 15-July 23, 2019

- 1 Center Funded
  - June 15, 2019

JCOIN Highlights: Overview

• FY18 Accelerator Supplement Highlighted Accomplishments
  • Surveys
  • Events
  • Products

• Research Hub Projects (Awards Made 7/15-7/23/2019)
  • Geographic Reach
  • Thematic Overview
  • Core Domains of Harmonized Measurement

• Capacity Building and Key Infrastructure Components (CTC & MAARC)
  • Stakeholder Outreach
  • Rapid Response Trials
  • Modeling Projects
  • Implementation Trials
JCOIN Highlights:

Accelerator Supplements: Surveys in the Field

- National Survey Opioid Treatment in Jails
  - Surveying over 200 jails in highly affected areas
  - Buy in from the National Sherriff’s Association
- National Survey of Practices in State Prisons
- National Survey of Practices in Drug Courts & Other Problem Solving Courts
- Survey of Practices for Veterans with Justice Involvement (VA)
JCOIN Highlights:
Accelerator Supplements: Products

**Public Health & Justice**
Forum on NDEWS

- **Four new datasets on relevant public policies by Legal Science**
  - Drug Induced Homicide
  - Involuntary Commitment
  - Medicaid Policies during Incarceration
  - Coverage of MAT by Medicaid

www.pdaps.org
https://network.ndews.org
JCOIN Highlights:

**Accelerator Supplements: Events**

Four Winning Teams Received Support to Assist Communities in Implementing Hackathon Solutions

Accelerated Timeline for Fielding Hub Studies with Harmonized Core Measures

**JCOIN Measurement Planning Meeting**

August 6-7, 2019
**JCOIN Highlights:**

# OF COMMUNITIES BY STATE IN JCOIN HUBS

**Puerto Rico**

**JCOIN Reach**
- 82 Communities
- 16 States/Territories
- 10 studies
- > 17,000 patients

*Note: “Community” for the purposes of this map is defined at the county level.*
**JCOIN Highlights:**

**JCOIN Research Hubs: Thematic Overview**

**STATE POLICY ROLLOUTS**
- **BAYSTATE (MA)**
  - Eval of new state policy mandating MOUD in jails
  - Jail (7)

- **NYSPI (NY)**
  - Practice guidelines / state impl strategy for opioid court model
  - Drug Court (10)

**CASE MANAGEMENT / PEER NAVIGATION**
- **U. OF CHICAGO (IL)**
  - Recovery case management + harm reduction
  - Jail (4) / Prison (2)

- **U. OF KY (KY)**
  - Telehealth / MOUD engagement for women
  - Jail (9)

- **CHESTNUT (IL)**
  - Adaptive version of Recovery Management Checkups
  - Jail (6)

- **TCU (TX, IL, NM)**
  - System-level impl strategy + Opioid Tx Linkage Model
  - Probation/Parole (18)

- **BROWN U. (RI, PA, NC)**
  - Org-level impl strategy + Peer support specialists
  - Probation/Parole (7)

**MOUD COMPARATIVE EFFECTIVENESS TRIALS**
- **NYU SOM (NY, CT, DE, NH, OR)**
  - XR-Naltrexone vs. XR-Buprenorphine (Sublocade)
  - Jail (5)

- **FRI (MD)**
  - XR-Naltrexone vs. XR-Buprenorphine (CAM2038/Brixadi)
  - Jail (10)

**ORGANIZATIONAL / SYSTEM IMPLEMENTATION + CLIENT LINKAGE INTERVENTION**
- **ORGANIZATIONAL / SYSTEM IMPLEMENTATION + CLIENT LINKAGE INTERVENTION**

**Awards Made**
- 7/15-7/23/2019
JCOIN Highlights:

JCOIN Measurement Planning Meeting (August 6-7, 2019):
Priority Domains for Harmonized Measurement

- **Substance Use**—Opioids, Alcohol, and other Drugs (includes overdose)
  - Self-report, administrative, biological, cascade of care

- **Criminal Behavior & Recidivism**
  - Self-report, administrative, criminogenic risk

- **Other Individual Characteristics**
  - **Examples:** HIV/HCV, mental health, suicidality, victimization history, attitudes toward MOUD

- **Clinical Intervention Characteristics and Fidelity**
  - **Examples:** Medication dosage, # of sessions delivered, etc.

- **Implementation Strategies & Organizational Climate**
  - **Examples:** Staff Attitudes, # and type of training, organizational policies, leadership, funding

- **Economic Measures**
  - **Examples:** Cost-effectiveness, service utilization, QALYs

- **Community Characteristics**
  - **Examples:** availability of treatment, transit times, socio-economic factors, laws

Finalized Plan Expected by Oct. 1

Novel Studies
JCOIN Highlights:
Capacity Building and Translational Infrastructure

Data & Analytics (MAARC—University of Chicago)
• Data Portal Integrating Multiple Existing Datasets
• Survey Research
• Modeling Projects & Analytic Support
  • Agent-based models, Predictive analytics, Network science, Geospatial approaches

Translation and Stakeholder Buy-In (CTC—George Mason University)
• Rapid Response Pilot Trials ($350k/year)
• Implementation Projects
• Key Stakeholder Input (create bidirectional feedback loops with network)
• Training for Researchers And Practitioners
HEAL Partnership Committee and Early Phase Pain Investigation Clinical Network

HEAL Multidisciplinary Working Group – August 21, 2019
Walter Koroshetz, NINDS Director
Barbara Karp, NINDS Division of Clinical Research
HEAL Partnership Committee Meeting
August 1, 2019

John Dunlop, Amgen
Mark Mintun, Lilly
Judith Paice, Northwestern University
Cheryl Stucky, Medical College of Wisconsin
Christin Veasley, Chronic Pain Research Alliance
Ashley Wittorf, AdvaMed

Steve Joffe, U Penn
Kenneth Verburg, Pfizer
Clifford Woolf, Harvard
Richard Moscicki, PhRMA
Dan Mellon, FDA/CDER
Dave Thomas, BIO
Overview of pain program
Preclinical animal model testing platform
Preclinical human based screening platform
1) Endpoint refinement/development to address gaps

2) Validated models configured into customized, asset-dependent flowcharts

3) Flexible decision-making process with input from participant

4) Rigor, confidentiality and IP protection

5) Commitment to appropriate data sharing
Optimization based on ECB input:

- Screening for opioid receptor binding & pharmacokinetic profiles
- Pharmacokinetics study based on stage of asset being tested
- Side effect profile assessed
- Assets are evaluated for abuse liability
- Need to identify appropriate non-evoked pain endpoints
Participation in PSPP

- PSPP is currently accepting assets for evaluation continuously, on an ongoing basis.
- Researchers from academic institutions or industry in the U.S. and internationally are eligible to submit assets for screening.
- To start the process, participants contact us for more information and to discuss research goals, resources, and timelines.
- A signed confidentiality agreement between NINDS and each potential participant is required before submission of agents for evaluation.
- Under NINDS direction, preclinical screening of test candidates is performed by contract facilities on a blinded and confidential basis.
- Since opening program up to participants two months ago, PSPP has had discussions with 20 parties.
NCATS Intramural Research Program in the HEAL Initiative: Developing Human-based Testing Platforms and Novel Drugs for Pain, Addiction, and Overdose

**NOT-TR-19-018** NCATS is accepting pre-proposal applications!

**Mission:** Speed and facilitate the development of new treatments for pain, opioid misuse and opioid overdose.
Generation of Human iPSCs for the NIH HEAL Initiative

1. 4-5ml blood draw
2. Isolate PBMCs
3. Reprogram and expand
4. Establish stable patient derived iPSCs

- 2-D Neuron Cultures
- 3-D Neural spheroids
- 3-D Minibrain Organoids
Human iPSC-Derived Neurons for Pain and Reward Pathways

Collaborators can work with NCATS Stem Cell Translation Lab to develop iPSC-derived cellular platforms for improved prediction of in vivo human effects of lead compounds.

Capabilities:

- Access to relevant human cell types
- Advanced imaging technologies for functional cell characterization
- High-throughput electrophysiology methods
- Measurement of signaling pathways, metabolism & specific targets
- Longitudinal tracking of cell behavior
- Combined single-cell transcriptomic & proteomic analyses

Sensory neurons (nociceptors) and other neuronal subtypes
High-content confocal, calcium imaging, optogenetics
High-density multi-electrode arrays 26,400 electrodes/well
Cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism
Multiple measurements over days, weeks or months
Drug response in individual nociceptors and other neuronal phenotypes
Development of Pharmacological Probes for Novel Targets

Access NCATS resources and expertise in assay development and quantitative high-throughput screening to identify promising compounds to modulate novel targets; optimize compound properties to probe novel targets.

Capabilities

- **HTS assay adaptation, development**
  - GPCR and ion channel assays and high-content image-based assays

- **Drug repurposing libraries**
  - All FDA approved compounds (>2,400), as well as >150,000 in annotated/diversity collections, HEAL-focused library

- **Counterscreen & confirmatory assays**

- **Cheminformatics platforms**
  - Molecular modeling and docking, Machine learning, High content image analysis

- **Medicinal chemistry**
  - Largest medicinal chemistry program at NIH, >30 fume hoods, >20,000 molecules made

- **ADMET Assays**
  - Aqueous kinetic solubility, rodent & human liver microsomal stability & PAMPA permeability
The goal of this FOA is to promote the development of in vitro microphysiological systems to model human nervous and non-nervous tissues that recapitulate the mechanisms or effects of nociception/pain-relevant signaling, addiction, or opioid use disorders (OUDs), and/or their respective therapies and treatments.
NIH HEAL
EPPIC-Net
Early Phase Pain
Investigation Clinical
Network

HEAL Multidisciplinary Working Group
August 21, 2019

Barbara Karp, MD
National Institute of Neurological Disorders and Stroke
HEAL Initiative Research Overview

Enhancing Pain Management

Pre-Clinical Research in Pain Management

Clinical Research in Pain Management

Expanding Therapeutic Options

Enhancing Treatments for Affected Newborns

Developing New/Improved Prevention & Treatment Strategies

Optimizing Effective Treatments

Improving Treatments for Misuse and Addiction
EPPIC Net Plans to Start Receiving Submissions on September 3

- Publicity implementation
- Webinar for potential applicants
- Trial run of submission process

Aug 17-24

- Refine submission process based on trial run
- Continue CCC/DCC/Hub& Spoke set up

Aug 25-Sept 1

OPEN FOR ASSET APPLICATIONS

Sept 3
Timeline for EPPIC-Net Launch

- **2019**
  - September: Preliminary application submission and review
  - October: Dossier preparation, submission and review
  - December: Protocol preparation, submission and review

- **2020**
  - January: FUNDING AND IMPLEMENTATION OF FIRST TRIALS
  - February: FUNDING AND IMPLEMENTATION OF FIRST TRIALS

NIH National Institutes of Health
Turning Discovery Into Health
Increased trial quality
Balanced portfolio
- Allows logical ordering of incoming trials
- Creates a pipeline for future trials
Stable infrastructure and research capacity
- Improved subspecialty input via working groups
- Stable funding for research and training
Improved data sharing
- Single data center with uniform governance
- Fosters the use of CDEs
Manages trials competing for similar patients
- Commitment to consider ALL eligible patients
Coordinates with non-profits, industry, and international partners
Trains the next generation of clinical trialists
EPPIC-NET Set-up Status

Infrastructure

Select CCC, DCC, Hubs

RFAs 19-NS-023, 024,025: Feb 2019

Hub re-issue
RFA 19-NS-036: July 2019

Application Templates and Processes

Preliminary Asset Template

Dossier Template

Protocol Template

IMPLEMENTATION

Review #1

Review #2

Review #3
Clinical Coordinating Center (CCC)
- Use a centralized IRB and Master Trial Agreements
- Match Hubs/Spokes to the protocol/asset
- Identify and train site investigators/staff
- Standardize CRFs and methodologies
- Work with DCC; develop SOPs and quality controls
- Distribute funds with NINDS oversight

Clinical Hubs & Spokes
- Identify individual investigators
- Conduct trials
- Collect and report data to DCC and CCC

Data Coordinating Center (DCC)
- Receive and centralize data
- Provide statistical/analysis reports
- Harmonize data, including that from BacPac, and for transfer to central repository when available
- Monitor safety/ provide reports to DSMB and other monitors
- Create and manage biorepository for samples throughout HEAL

NIH
- Interact with all EPPIC-Net components
- Provide oversight of budget and milestones

Funding for infra-structure components are U24 Cooperative Agreements
EPPIC-NET Application Templates and Processes

**Preliminary template**
- Completed with HPC/MDWG input
- Packet with information sheet, application, and instructions posted

**Dossier template**
- Completed with HPC/MDWG input
- Contract in place to prepare dossiers

**Protocol template**
- Protocol written by CCC with input from all stake-holders
- Based on NIH/FDA Clinical Trial Protocol Template

**Review 1, 2, 3**
- Review criteria for each stage finalized
- Will be incorporated into ROA and posted on EPPIC-Net website
# EPPIC NET - Clinical Trial Selection

<table>
<thead>
<tr>
<th>WHAT:</th>
<th>WHO:</th>
<th>AWARD:</th>
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</thead>
<tbody>
<tr>
<td>Preliminary Asset Application</td>
<td>Brief Asset Data</td>
<td>Applicant</td>
</tr>
<tr>
<td>In Depth Asset Review: Dossier</td>
<td>Complete Asset Dossier</td>
<td>Applicant and NINDS Contractor</td>
</tr>
<tr>
<td>Clinical Trial Protocol review</td>
<td>Clinical Trial Protocol</td>
<td>EPPIC-Net CCC* (with DCC, Hub PIs and Applicant)</td>
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**Objective Review Panel**
Evaluates assets based on template, full dossiers, and clinical protocols

**MDWG**
**NINDS Council**
**NIH HEAL Executive Committee**

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**Other Transaction Awards are used to fund EPPIC-Net Clinical Trials**

*OT award made to CCC for distribution to Hubs/spokes for trial conduct. Asset owner does not receive funds; does receive access to EPPIC-Net for asset clinical trial.*
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, 11 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 from EPPIC-Net and BacPac for later transfer to HEAL central repository
- EPPIC-Net DCC will serve as the biosample repository for all HEAL programs
- FNIH and the HEAL Partnership Committee will encourage submission of assets for EPPIC-Net clinical trials
MDWG Assessment
Opportunity for MDWG Input to Guide HEAL Research

• Does the combined ACT NOW and HEALthy BCD portfolio reflect appropriate research distribution in terms of condition, recruitment/retention strategy, exposures of patient population, etc.?

• Are there noticeable research gaps that are not being addressed?

• Are there ways to integrate ACT NOW and HEALthy BCD that have not been considered?

• Will the proposed research meet the bold, trans-NIH goals to address opioid misuse and addiction?
Session 6: Next Steps
Summary of the Day’s Discussion and Plans for Tomorrow’s Meeting

Rebecca Baker, Ph.D.
Director, HEAL Initiative, Office of the Director