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

August 21, 2019

Wilson Hall, NIH Campus

Bethesda MD

National Institutes of Health

Turning Discovery Into Health

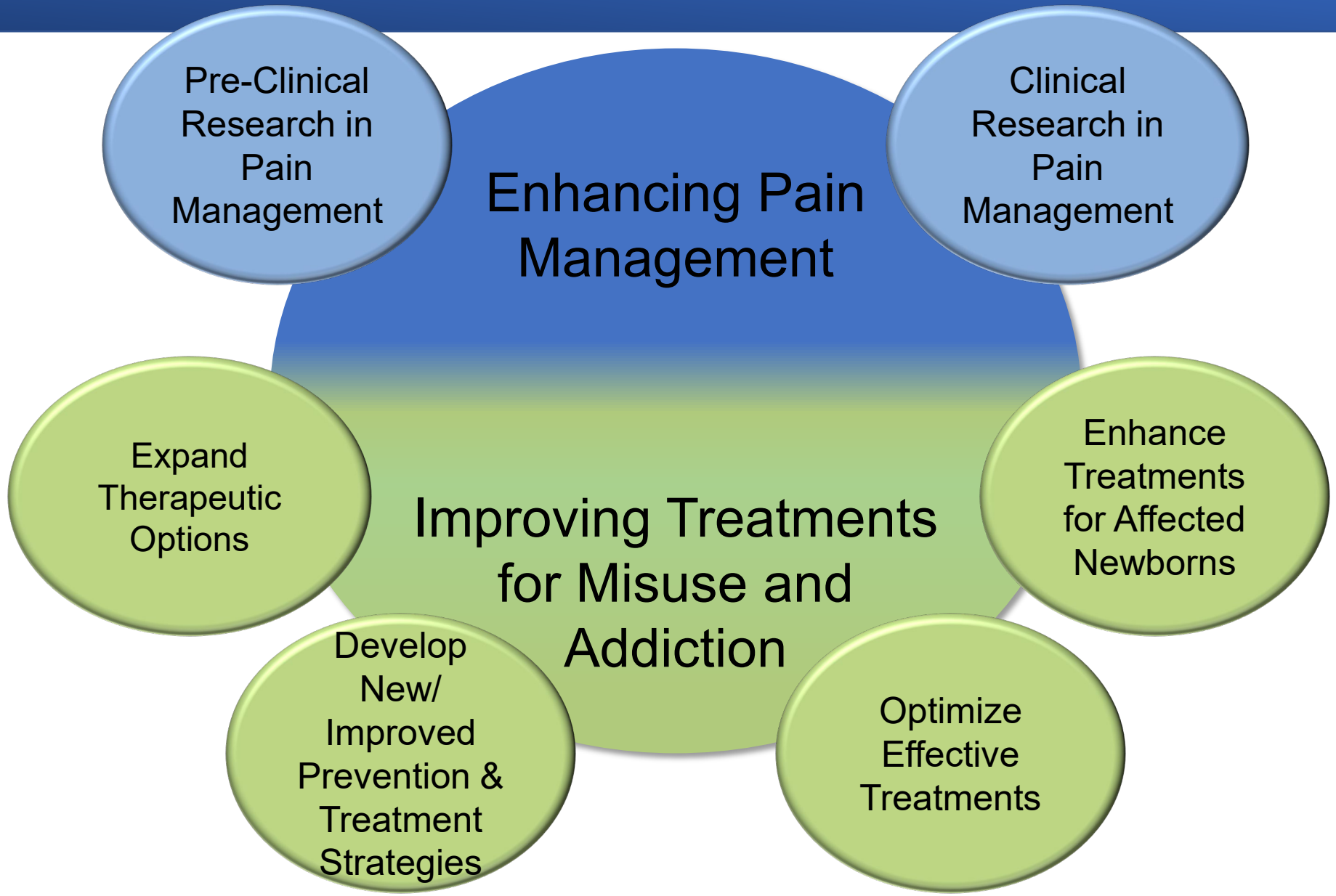
Session 1: Overview and NIH HEAL Initiative Activities Underway

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

Francis S. Collins, MD, PhD

Director, National Institutes of Health

HEAL Initiative Research Overview



Introduction to Agenda

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

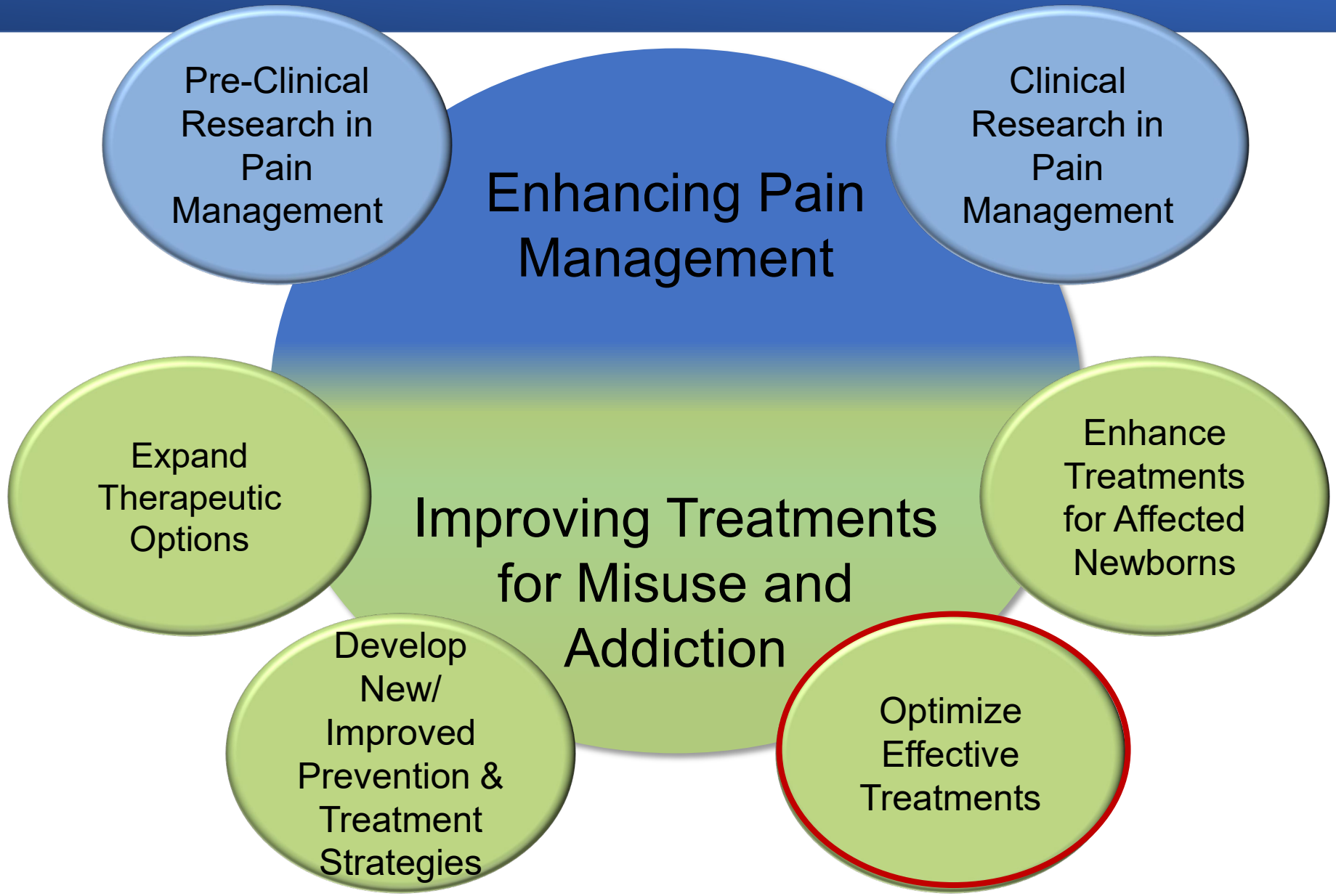
The Justice Community Opioid Innovation Network (JCOIN)

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

NIH National Institutes of Health
Turning Discovery Into Health

HEAL Initiative Research Overview

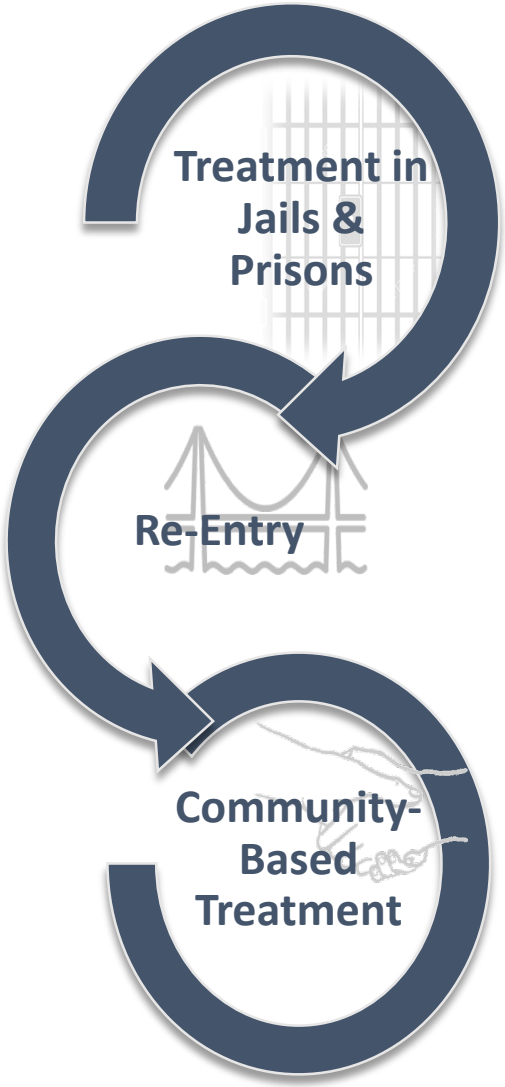


Optimize Effective Treatments:

- 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

Novel Studies

Accelerator Supplements
FY18/19 Only
($5.5M)

- Rapid Studies
- Baseline Data Collection: National Surveys
- Early Infrastructure

12 Projects Funded Sept. 2018 – May 2019

Research Hubs
UG1 ($23M/Y)

- Multi-site Studies
- Each = Large Scale Project in 5+ Communities
- Cascade of Care Focus
- Each has Justice & Treatment Partner

10 Projects Funded
July 15-July 23, 2019

Supportive Infrastructure

Coordination and Translation Center
CTC
U2C ($3.5M/Y)

- Implementation Science & Translational Outreach

1 Center Funded
June 15, 2019

Methodology and Advanced Analytics Resource Center
MAARC
U2C ($3.5M/Y)

- Data Infrastructure

1 Center Funded
June 15, 2019

https://www.nih.gov/news-events/news-releases/nih-establishes-network-improve-opioid-addiction-treatment-criminal-justice-settings

JCOIN Highlights: Overview

Novel Studies

- 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

Supportive Infrastructure

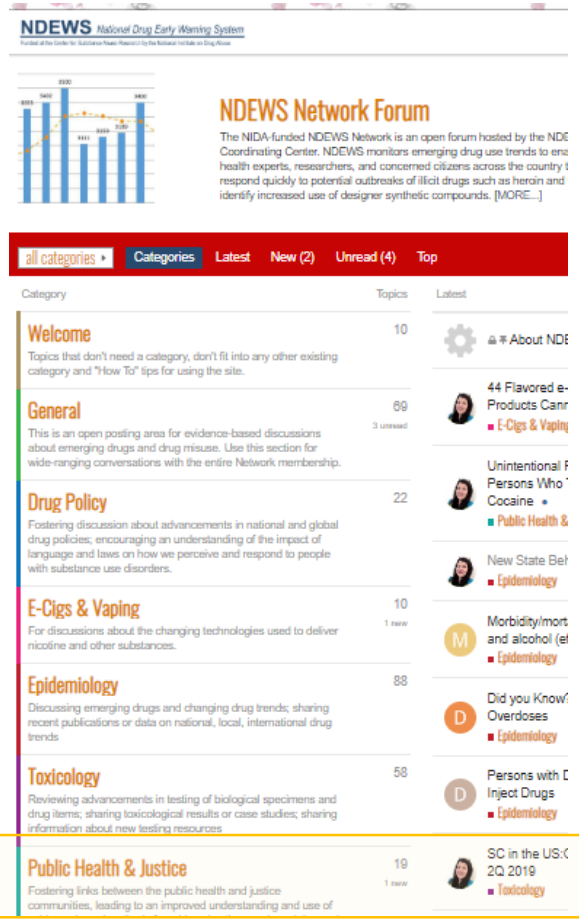
- Capacity Building and Key Infrastructure Components (CTC & MAARC)
  - Stakeholder Outreach
  - Rapid Response Trials
  - Modeling Projects
  - Implementation Trials

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)

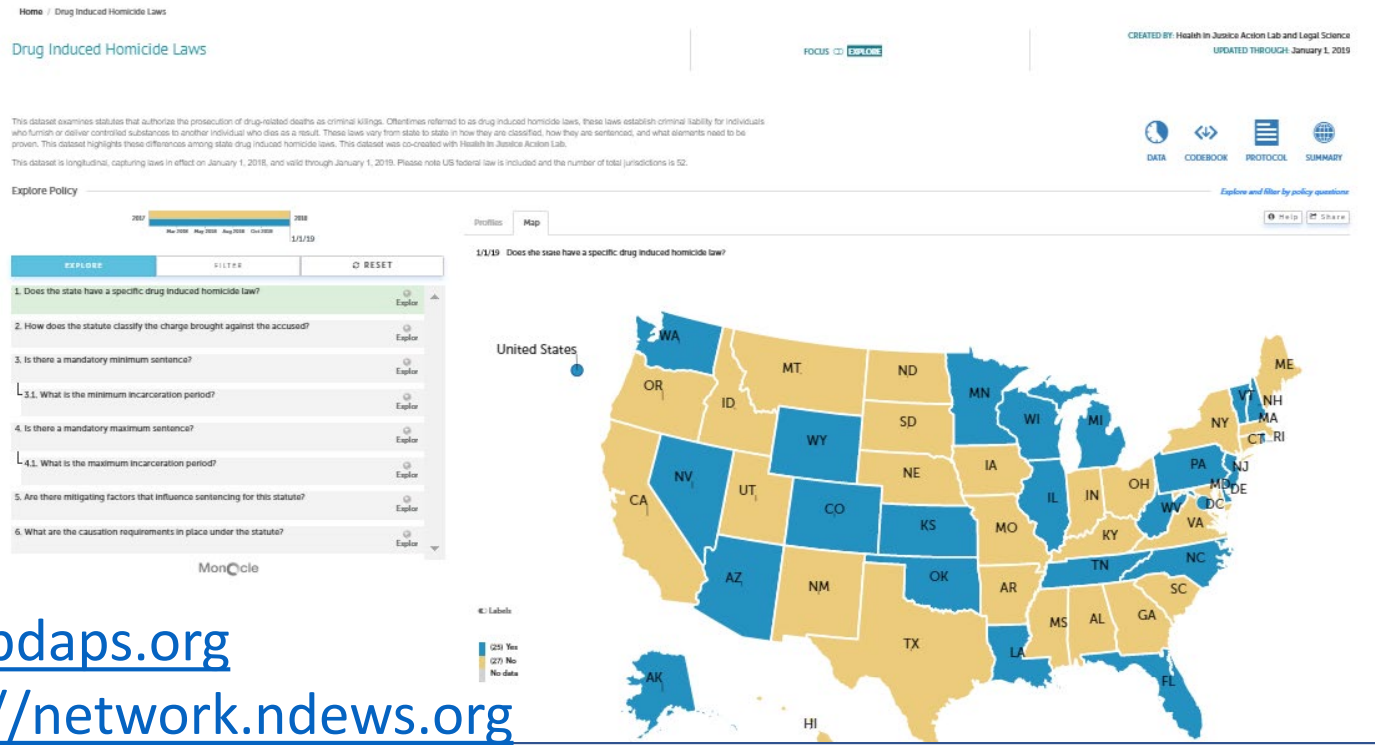
JCOIN Highlights:
Accelerator Supplements: Products

✓Public Health & Justice Forum on NDEWS



✓Four new datasets on relevant public policies by Legal Science

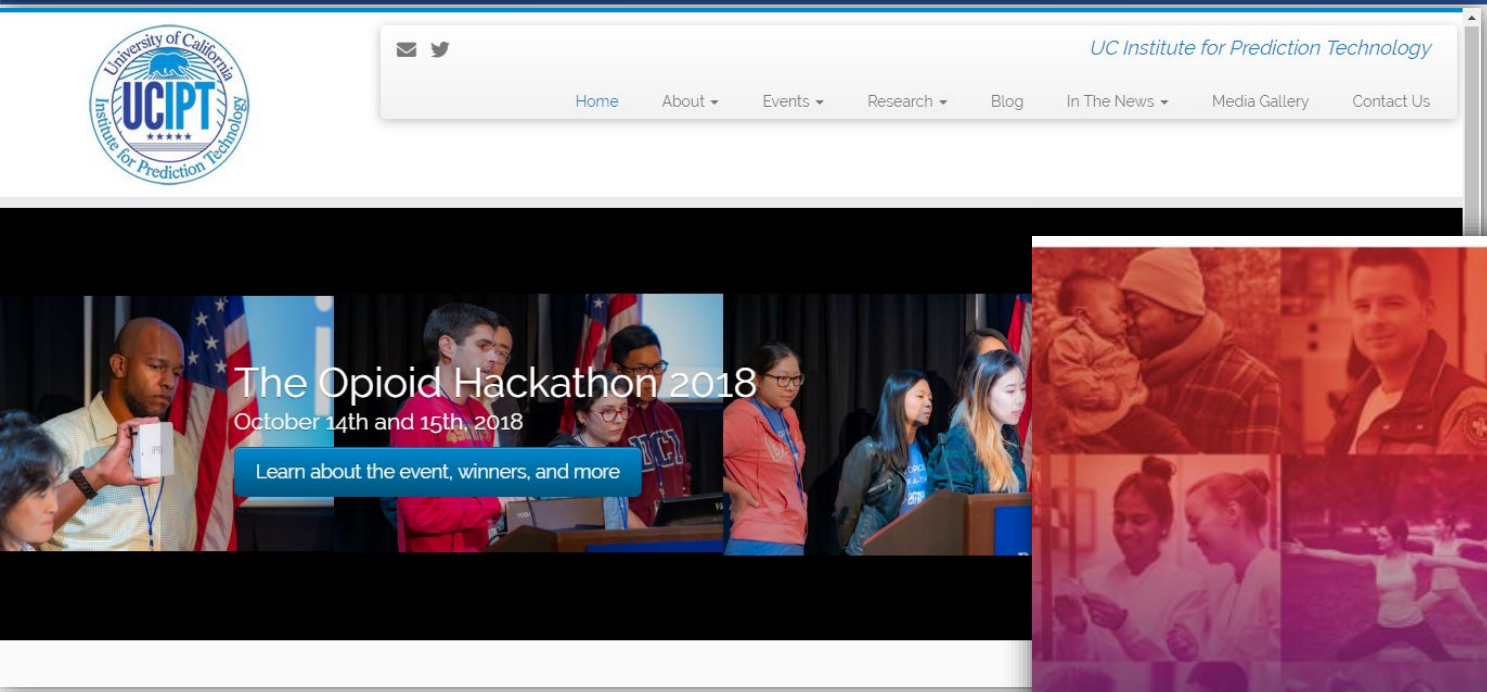
- Drug Induced Homicide
- Involuntary Commitment
- Medicaid Policies during Incarceration
- Coverage of MAT by Medicaid



www.pdaps.org

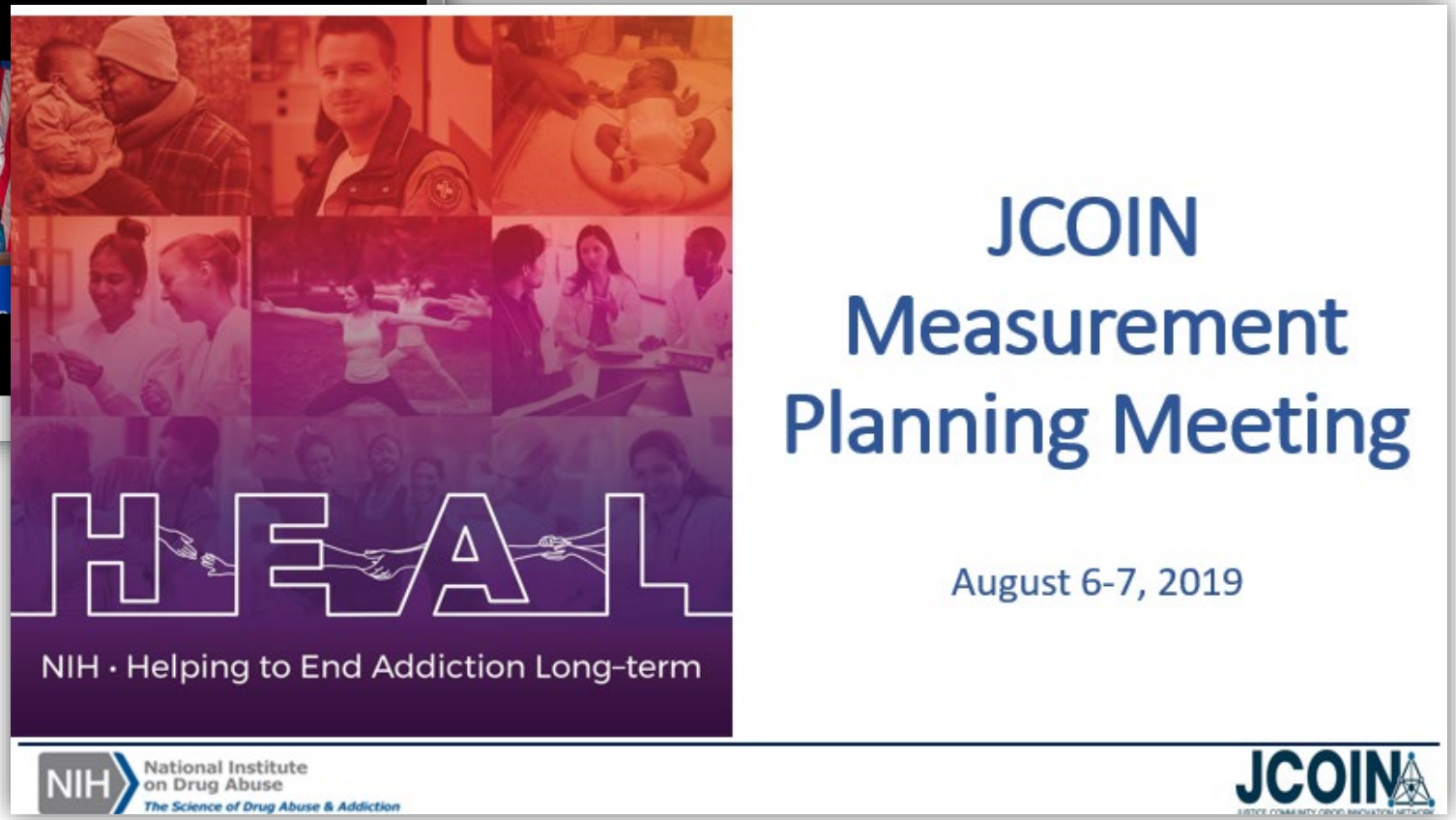
https://network.ndews.org

JCOIN Highlights:
Accelerator Supplements: Events

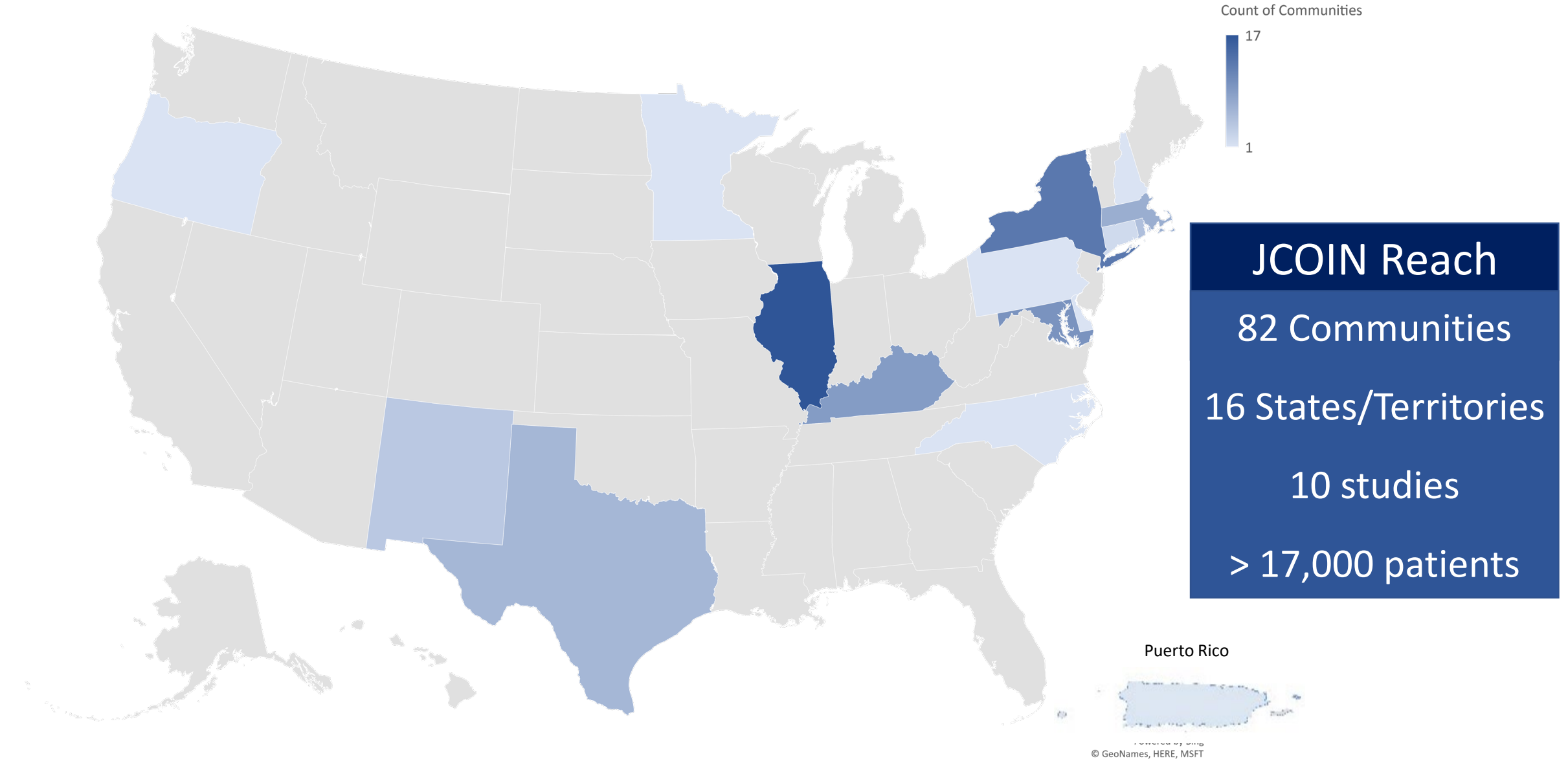


Four Winning Teams Received Support to Assist Communities in Implementing Hackathon Solutions

Accelerated Timeline for Fielding Hub Studies with Harmonized Core Measures



JCOIN Highlights:
OF COMMUNITIES BY STATE IN JCOIN HUBS



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)

CHESTNUT (IL)
Adaptive version of Recovery Management Checkups

Jail (6)

U. Of KY (KY)
Telehealth / MOUD engagement for women

Jail (9)

YALE (CT, MN, NY, NC, PR)
Primary care + CHWs for OUD treatment engagement

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

Awards Made 7/15-7/23/2019

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

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

DISCUSSION

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

National Institutes of Health
Turning Discovery Into Health

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

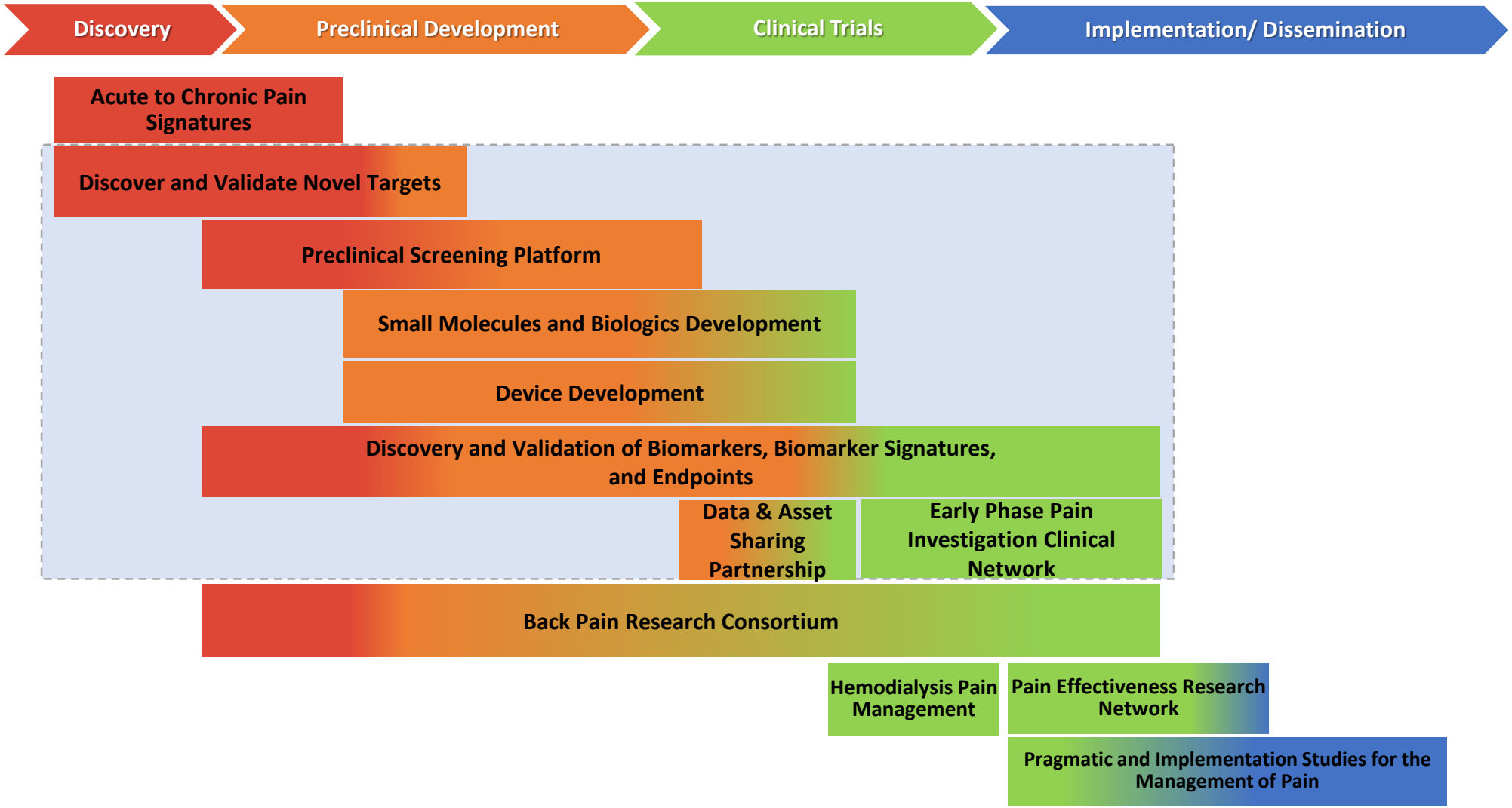
Steve Joffe, U Penn
Kenneth Verburg, Pfizer
Clifford Woolf, Harvard
Richard Moscicki, PhRMA
Dan Mellon, FDA/CDER
Dave Thomas, BIO

HEAL Partnership Committee Meeting
August 1, 2019

Agenda

Overview of pain program
Preclinical animal model testing platform
Preclinical human based screening platform

HEAL Programs for Pain



Preclinical Screening Platform for Pain (PSPP): Key Elements

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

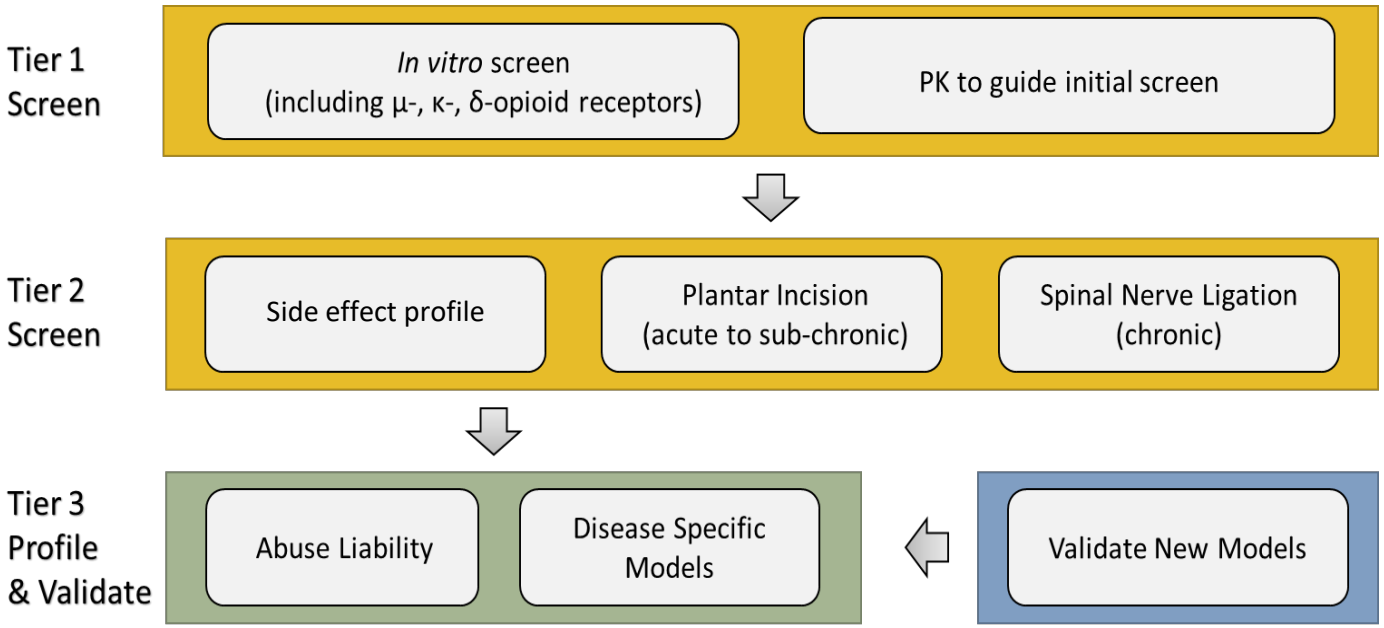
4) Rigor, confidentiality and IP protection

5) Commitment to appropriate data sharing

Testing Strategy: Screen, Profile, and Validate

➢ **Optimization based on ECB input:**

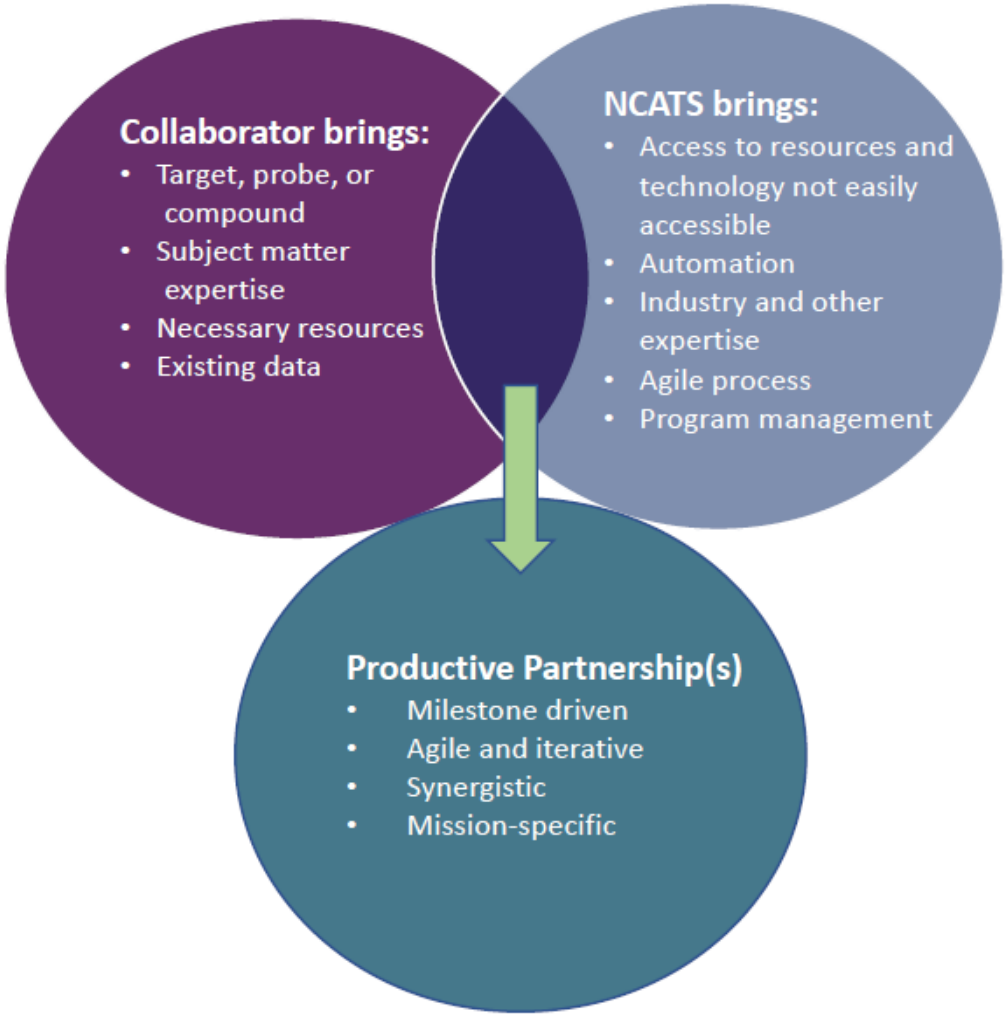
- Screening for opioid receptor binding & pharmacokinetic profiles
- Pharmacokinetics study based on stage of asset being tested
- Side effect profile assessed
- Assets are evaluated for abuse liability
- Need to identify appropriate non-evoked pain endpoints



Participation in PSPP

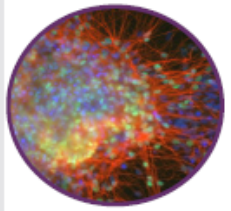
- PSPP is currently accepting assets for evaluation continuously, on an ongoing basis
- Researchers from academic institutions or industry in the U.S. and internationally are eligible to submit assets for screening
- To start the process, participants contact us for more information and to discuss research 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

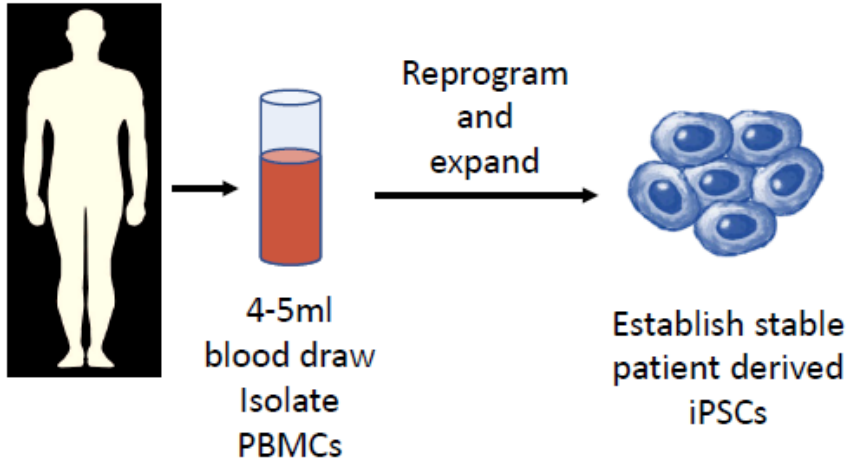


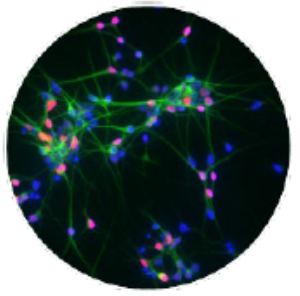
NOT-TR-19-018 *NCATS is accepting pre-proposal applications!*

Mission: Speed and facilitate the development of new treatments for pain, opioid misuse and opioid overdose

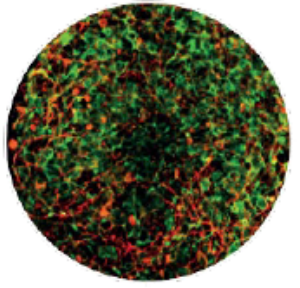


Generation of Human iPSCs for the NIH HEAL Initiative

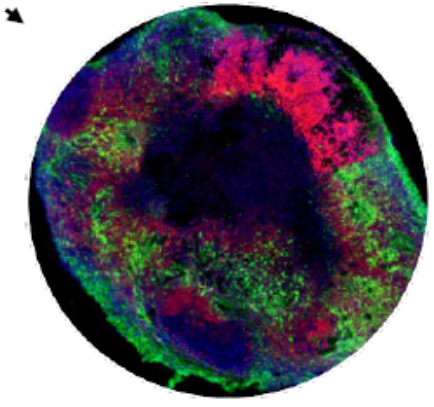




2-D Neuron Cultures

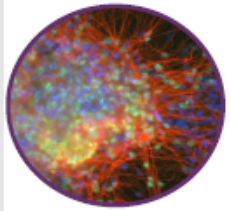


3-D Neural spheroids



3-D Minibrain Organoids

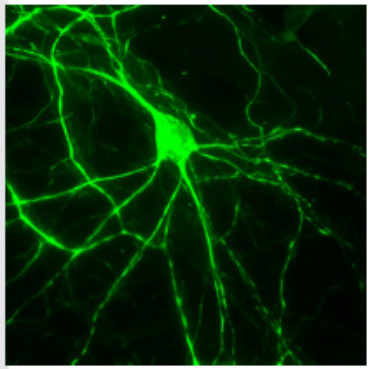
National Center
for Advancing
Translational Sciences



Human iPSC-Derived Neurons for Pain and Reward Pathways

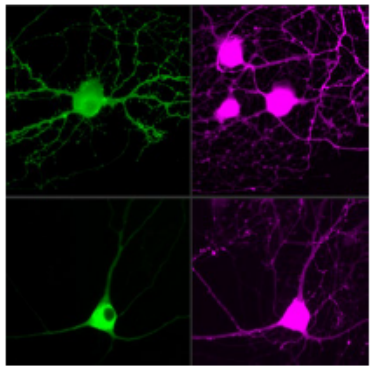
Collaborators can work with NCATS Stem Cell Translation Lab to develop iPSC-derived cellular platforms for improved prediction of *in vivo* human effects of lead compounds

Capabilities:



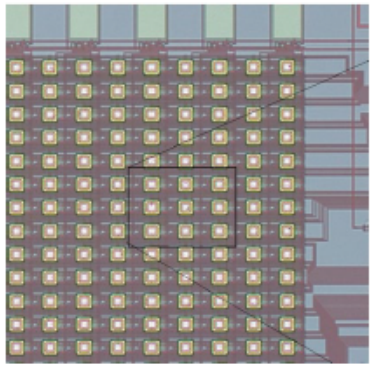
Access to relevant human cell types

Sensory neurons (nociceptors) and other neuronal subtypes



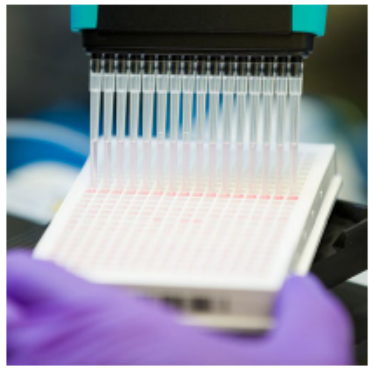
Advanced imaging technologies for functional cell characterization

High-content confocal, calcium imaging, optogenetics



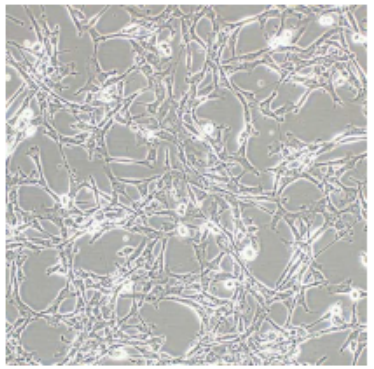
High-throughput electrophysiology methods

High-density multi-electrode arrays 26,400 electrodes/well



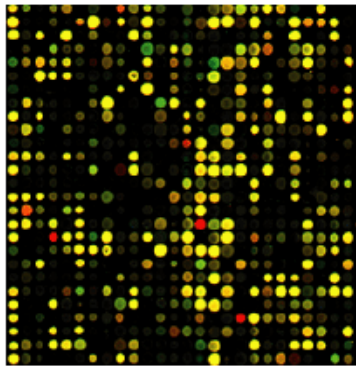
Measurement of signaling pathways, metabolism & specific targets

Cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism



Longitudinal tracking of cell behavior

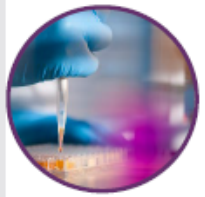
Multiple measurements over days, weeks or months



Combined single-cell transcriptomic & proteomic analyses

Drug response in individual nociceptors and other neuronal phenotypes

National Center for Advancing Translational Sciences



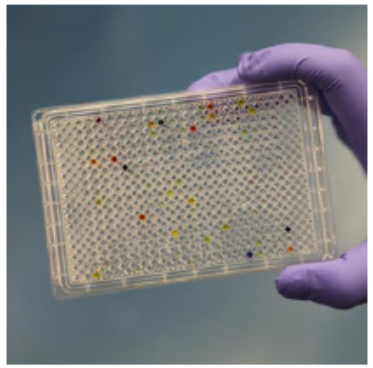
Development of Pharmacological Probes for Novel Targets

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

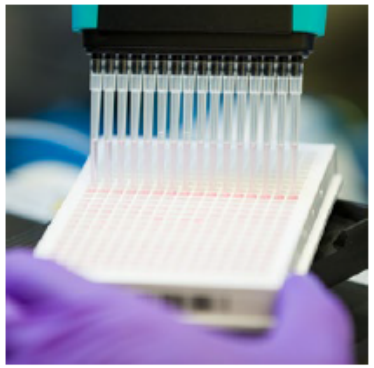
HTS assay adaptation, development

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

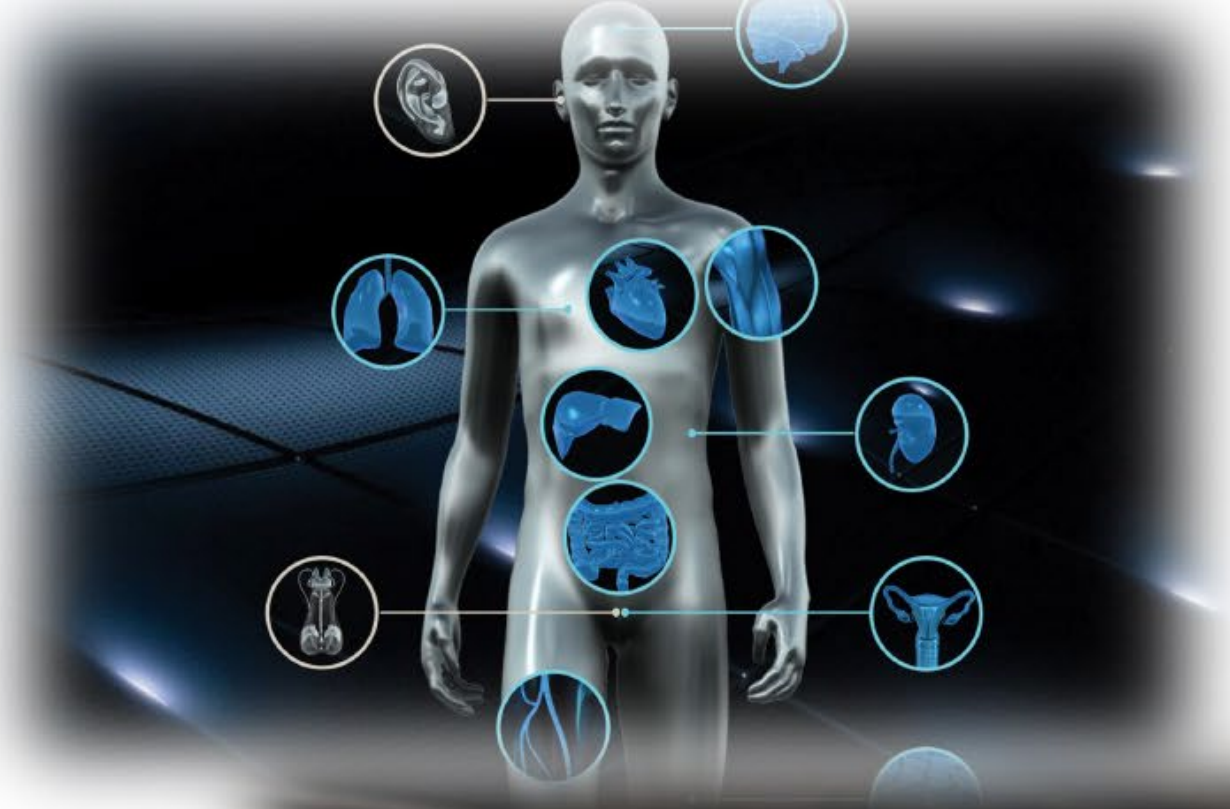
Aqueous kinetic solubility, rodent & human liver microsomal stability & PAMPA permeability

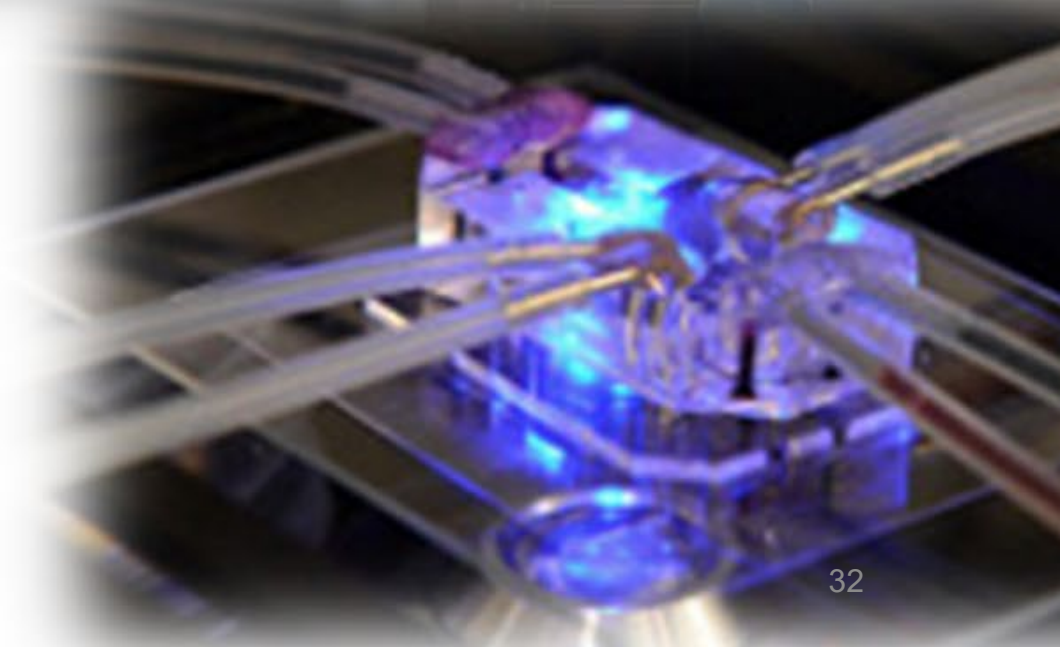
National Center for Advancing Translational Sciences

Tissue Chip

RFA TR-19-003

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.





National Center for Advancing Translational Sciences

NIH HEAL EPPIC-Net Early Phase Pain Investigation Clinical Network

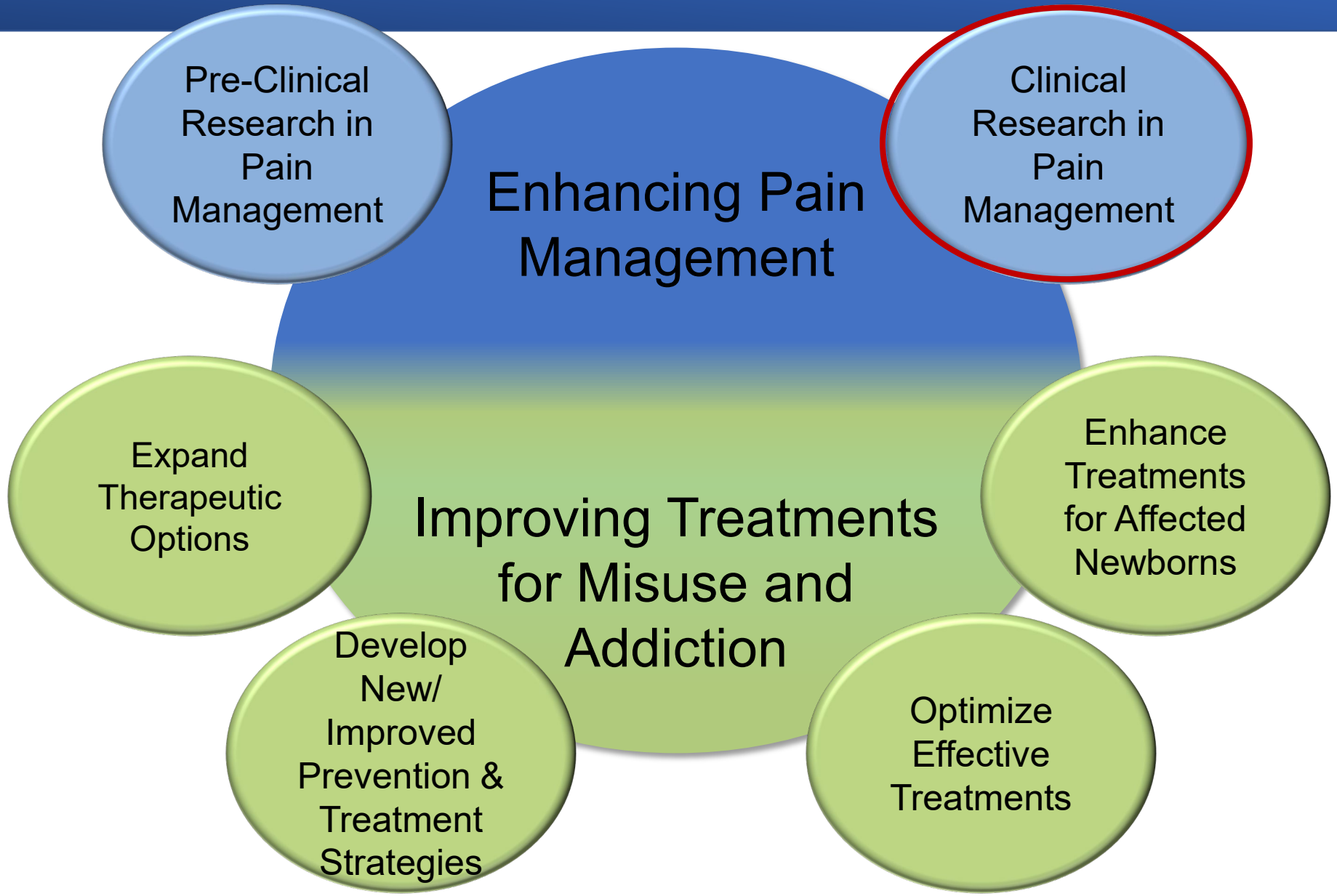
HEAL Multidisciplinary Working Group

August 21, 2019

Barbara Karp, MD
National Institute of Neurological Disorders and Stroke

NIH National Institutes of Health
Turning Discovery Into Health

HEAL Initiative Research Overview



EPPIC Net Plans to Start Receiving Submissions on September 3

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

Aug17-24

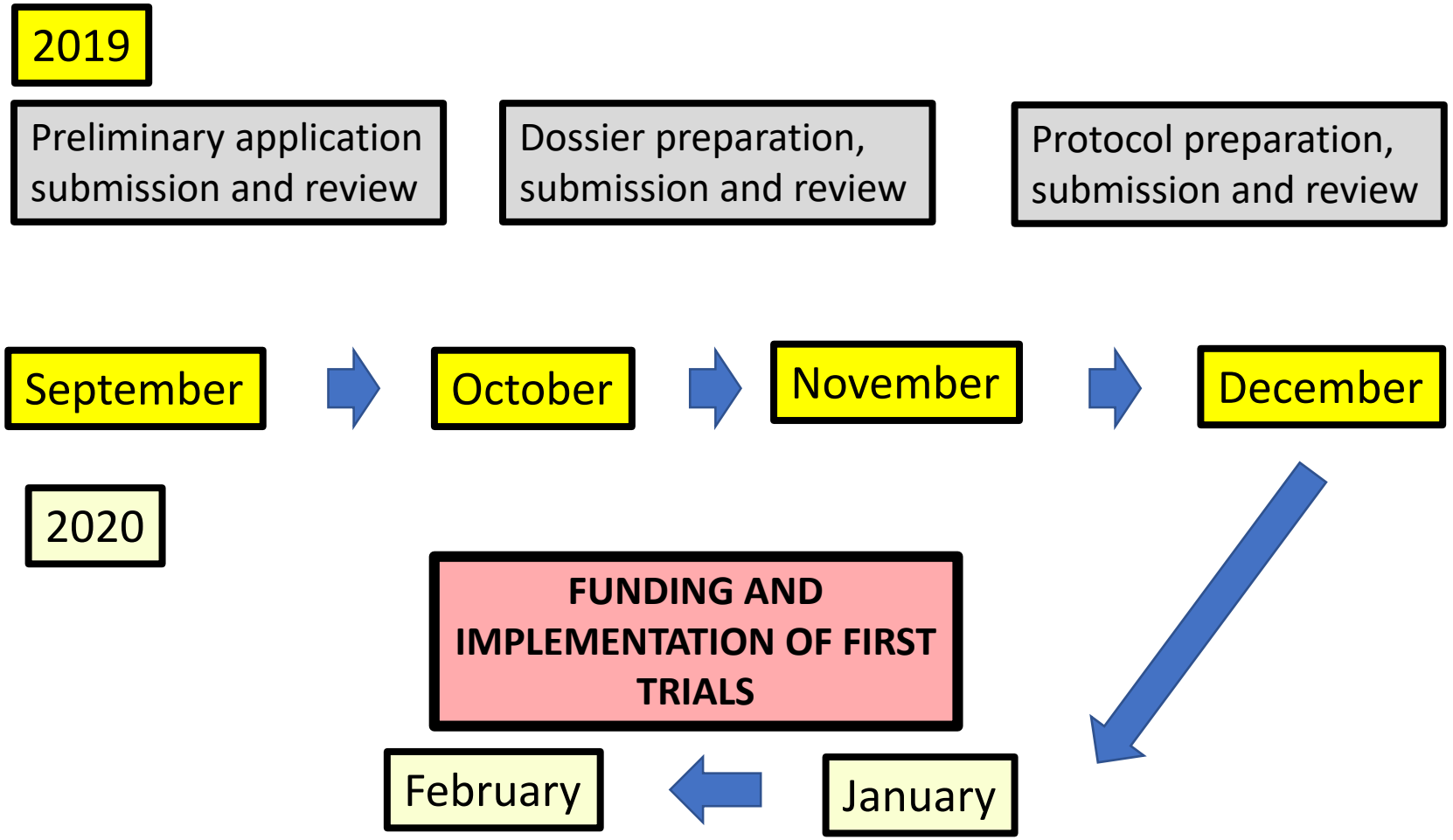
- Refine submission process based on trial run
- Continue CCC/DCC/Hub& Spoke set up

Aug 25-Sept 1

OPEN FOR ASSET APPLICATIONS

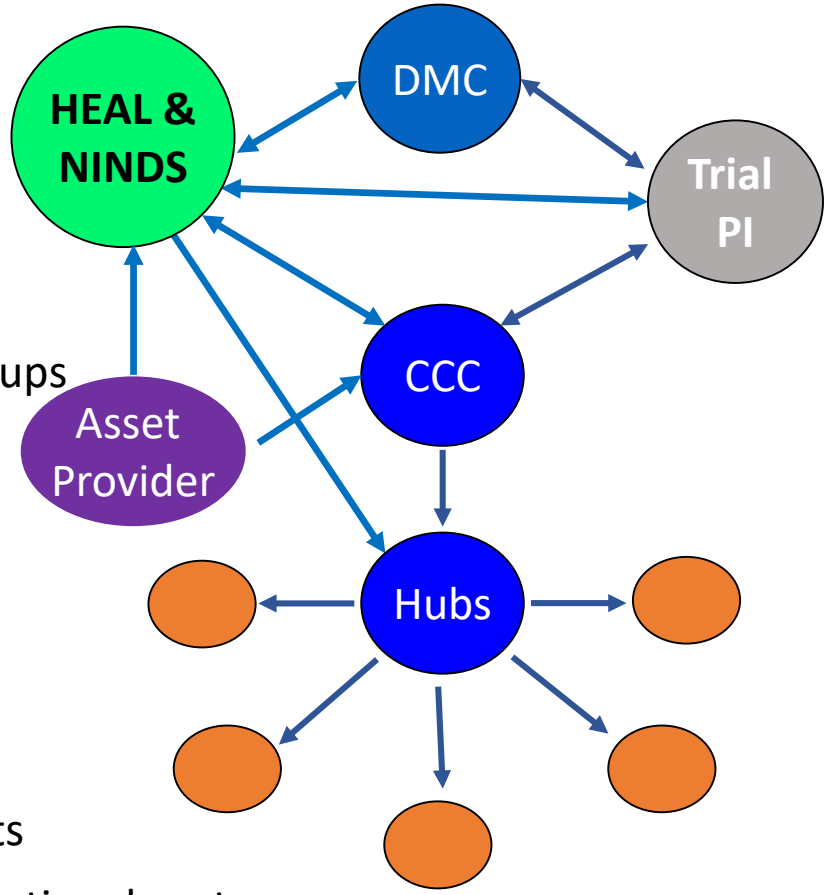
Sept 3

Timeline for EPPIC-Net Launch



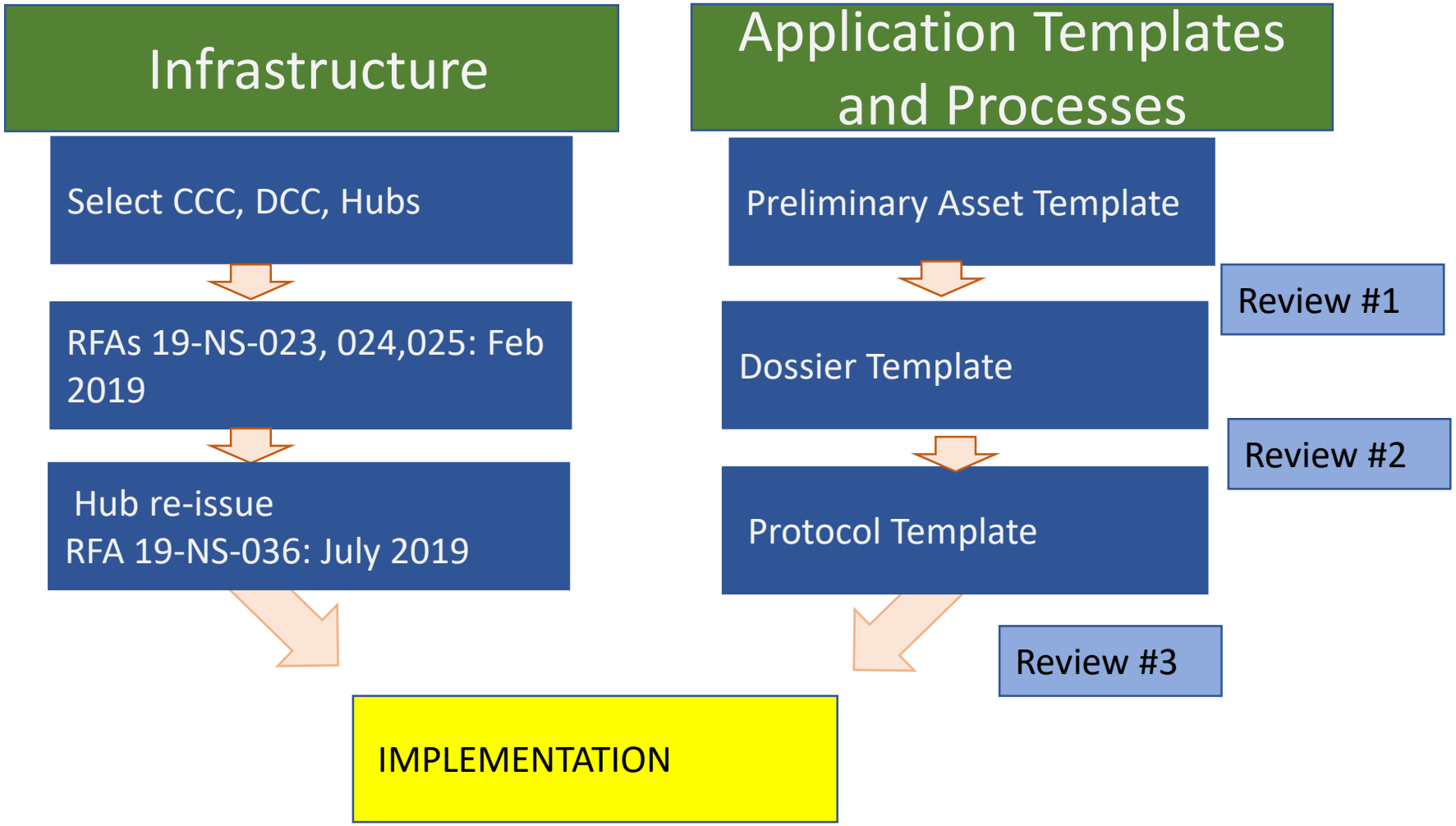
Organizational and Funding Structure

- 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



Eventual phase 3 trial by Provider

EPPIC-NET Set-up Status



EPPIC NET - Building a Clinical Network

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

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

Clinical Hubs &Spokes

- Identify individual investigators
- Conduct trials
- Collect and report data to DCC and CCC

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
- https://grants.nih.gov/policy/clinical-trials/protocol-template.htm

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

	WHAT:	WHO:	AWARD:
Preliminary Asset Application	Brief Asset Data	Applicant	NO
In Depth Asset Review: Dossier	Complete Asset Dossier	Applicant and NINDS Contractor	NO
Clinical Trial Protocol review	Clinical Trial Protocol	EPPIC-Net CCC* (with DCC, Hub PIs and Applicant)	YES

Objective Review Panel
Evaluates assets based on template, full dossiers, and clinical protocols

MDWG

NINDS Council

NIH HEAL Executive Committee

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

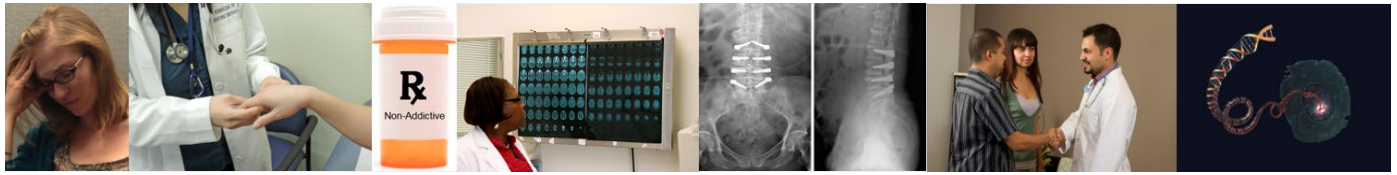
Improve quality, consistency, efficiency of early phase pain clinical trials

- **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

FNIH
Foundation for the National Institutes of Health



DISCUSSION

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 5: Summary Discussion

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