

Session 3:

Presentation of Selected HEAL Program Areas to Enhance Pain Management



Discover and Validate Novel Targets for Safe and Effective Pain Treatment

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National Institutes of Health
Turning Discovery Into Health



Discover and Validate Novel Targets for Safe and Effective Pain Treatment: Beginnings

- Consulted with experts from across government, industry, and academia to determine the pharmacological areas that could be best addressed through public-private partnerships
- Concern that basic science proposals identify new targets, but do not contain rigorous validation studies
 - Burden falls to industry to validate
 - Increases the cost and risk of investment in new targets
 - Examples of validation: multiple animal models of pain, knockout models, confirming that the target is present in human tissues
- Goal: Align fundamental studies of pain pathways with the needs of companies and academics developing therapeutics to have well validated targets to work on.

June 5, 2017

Full Summary — Medications Development for Opioid Use Disorders and Overdose Prevention and Reversal

Cutting Edge Science Meeting Series to End the Opioid Crisis

June 16, 2017

Full Summary — Development of Safe, Effective, and Non-Addictive Pain Treatments

Cutting Edge Science Meeting Series to End the Opioid Crisis

July 7, 2017

Full Summary — Understanding the Neurobiological Mechanisms of Pain

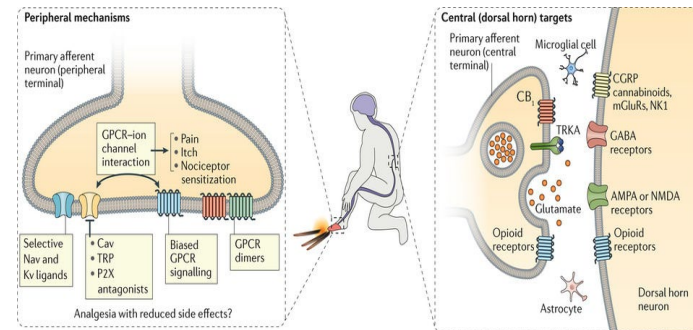
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- **Purpose:** Promote the discovery and validation of novel therapeutic targets
- **Focus:** Link basic science discovery of targets that can be used to develop treatments with rigorous validation studies to demonstrate robustness as a pain treatment target
- **Goal:** Lower risk of adopting the target in translational projects to develop small molecules, biologics, natural substances, or devices that interact with this target for new pain treatments
 - Welcome projects to identify novel targets in specific populations such as women, children, older adults or other underrepresented groups
 - Not focused on translational research to develop new medical devices or any one or group of pain conditions



Discover and Validate Novel Targets for Safe and Effective Pain Treatment: Examples

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

Preclinical Screening Platform for Pain (PPSP)

Amir Tamiz, PhD
Associate Director,
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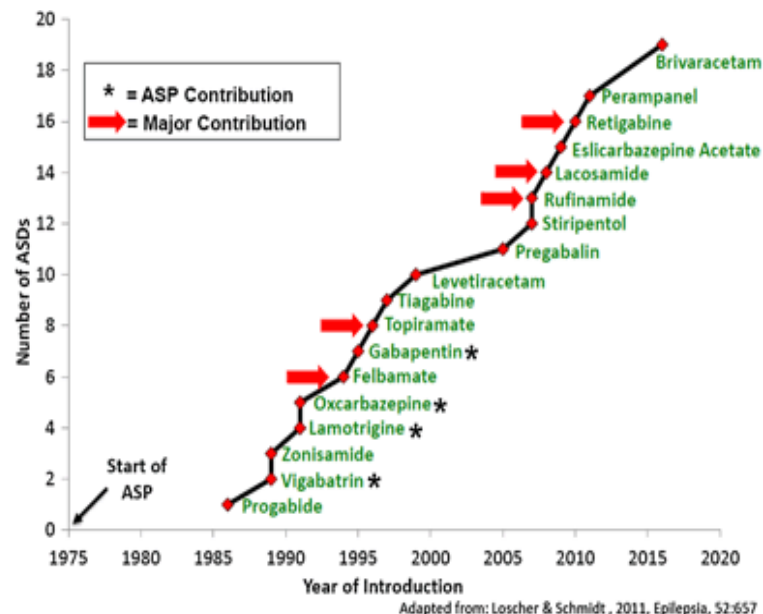


Preclinical Screening Platform for Pain (PSPP): Mission and Strategy

- Accelerate the Discovery and Pre-Clinical Development of Non-Addictive Treatments for Pain
- Establish a sophisticated preclinical testing program to help identify non-addictive pain treatments with ever increasing power to predict efficacy in human trials
- Acquire models for specific pain conditions and generate predictive endpoints
- Generate high quality data in pain models to support advancement of promising treatments towards clinical trials

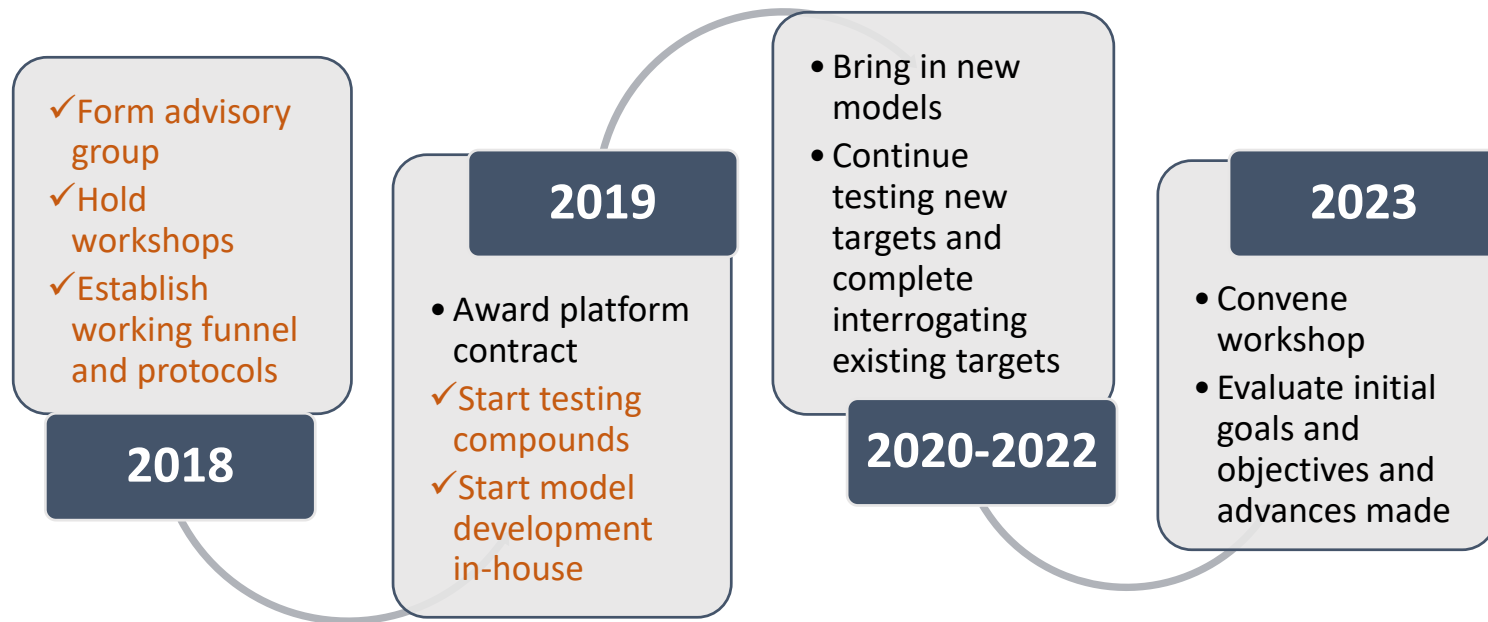
A Proven Model to Spur Innovative Therapies

- Based on successful NINDS-funded Anticonvulsant Screening Program (ASP*)
- Contract mechanism to screen and profile submitted compounds/devices in a battery of preclinical models of acute and chronic pain
- Public database to publish best practices and high quality data



*Currently known as the Epilepsy Therapy Screening Program (ETSP)

Timelines (2018-2023)



Developing Drugs and Testing Platforms for Pain, Addiction and Overdose

Joni Rutter, PhD

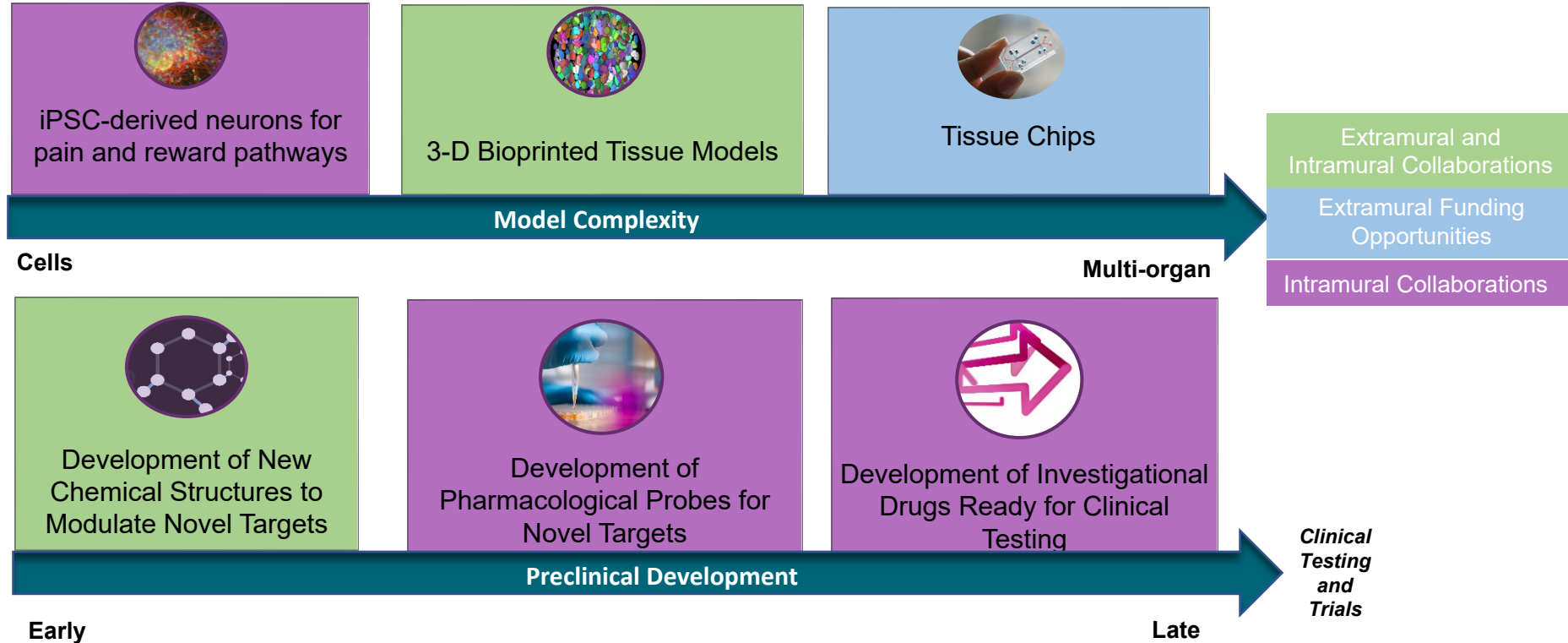
Deputy Director

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Developing Drugs and Testing Platforms for Pain, Addiction and Overdose





Extramural Opportunities and Intramural Collaborations through NCATS

Intramural collaborations with NCATS - to enable development of new experimental therapeutics

- Not an extramural grant - no funding provided to collaborator's institution
- Team-based: You (who have existing data, disease knowledge and novel therapeutic hypothesis) + NCATS (preclinical drug development expertise and laboratory capabilities)
- Efficiency: state of the art technology and milestone-driven collaboration plans

Extramural funding opportunities

- RFA-TR-19-005: HEAL Initiative: Biofabricated 3D Tissue Models of Nociception, Opioid Use Disorder and Overdose for Drug Screening
- RFA-TR-19-003: HEAL Initiative: Tissue Chips to Model Nociception, Addiction, and Overdose
- NOT-TR-18-031: HEAL Initiative: Announcement of the NCATS ASPIRE Design Challenges to Develop Innovative and Catalytic Approaches Towards Solving the Opioid Crisis

Questions/Discussion

Early Phase Pain Investigation Clinical Network (EPPIC-Net)

Clinton Wright, MD

Director, Division of Clinical Research

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Early Phase Pain Investigation Clinical Network (EPPIC-Net)

Mission and Goals

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

Goals

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

EPPIC-Net Infrastructure

Data Coordination Center (DCC)

- Statistical expertise
- Trial expertise

Repositories:
Industry and HEAL
biosamples,
neuroimaging, and
data

Clinical Coordination Center (CCC)

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

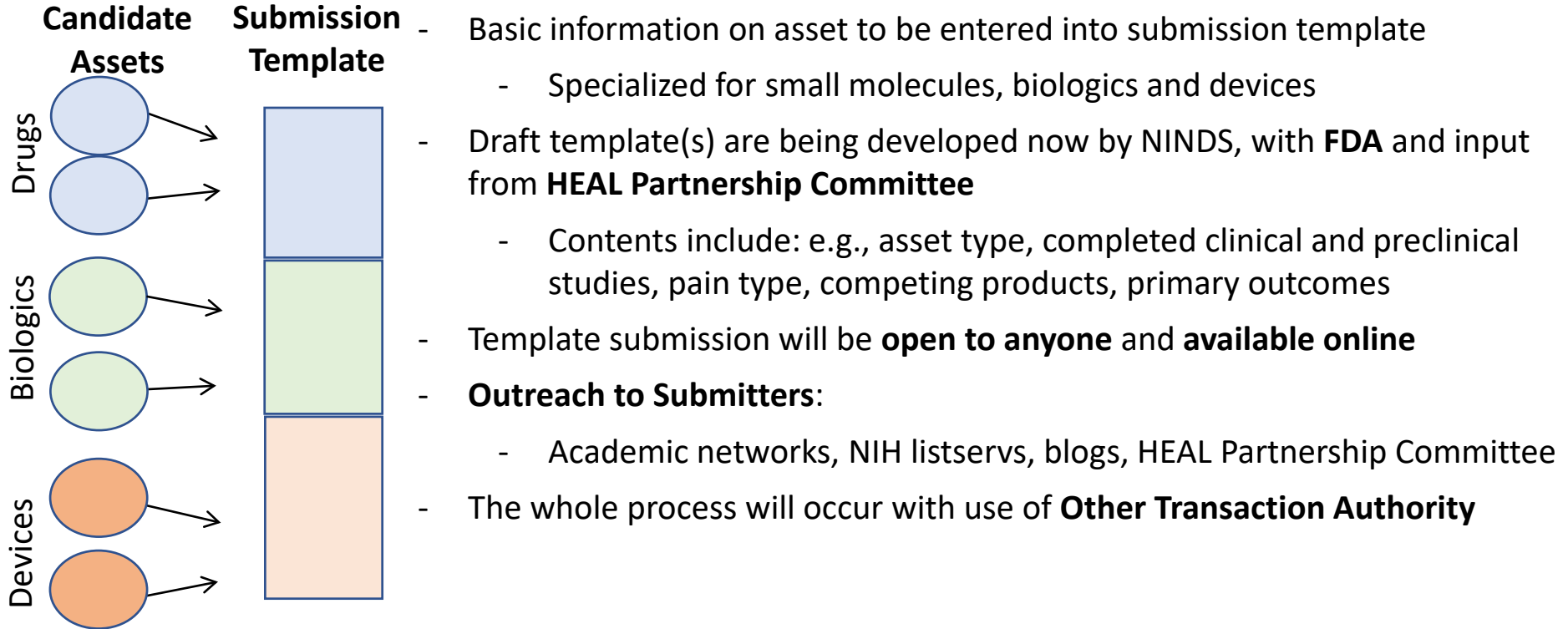
10 Specialized Clinical Centers (hubs + spokes)

- Protocol design (with CCC)
- Trial execution
- Ready access to patient populations and expertise in multiple specific pain conditions, including low back pain

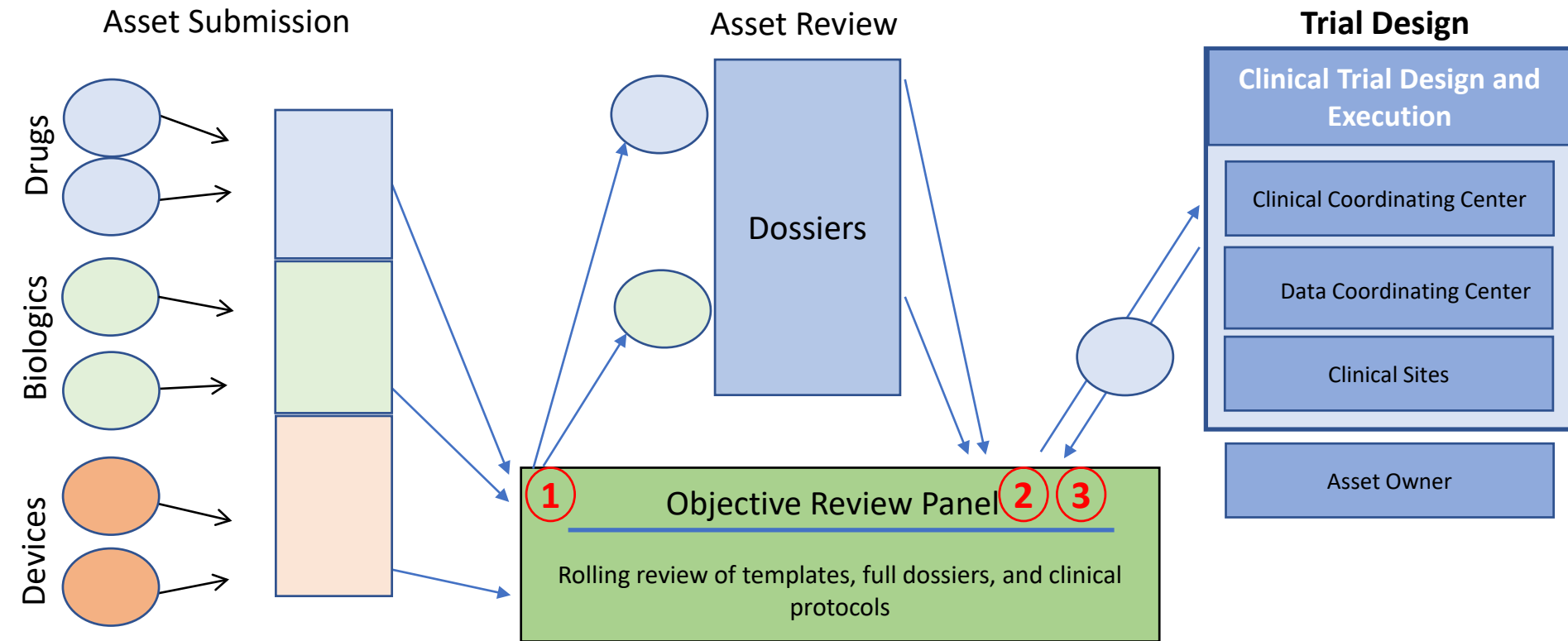
Coordination centers and clinical sites all solicited through funding opportunities, planned to award at May council



EPPIC-Net Process: Asset Submission

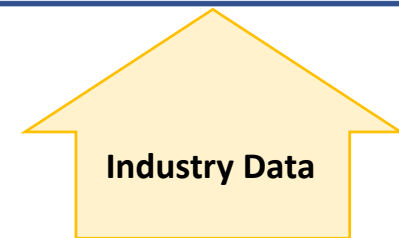
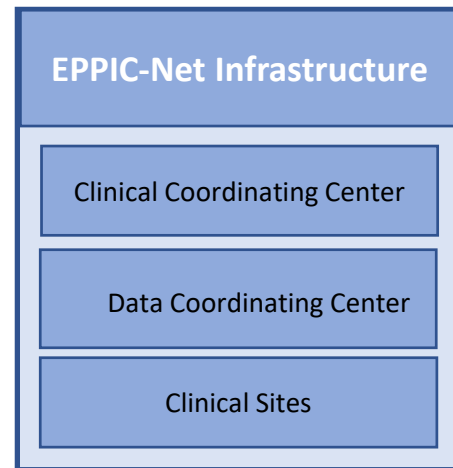
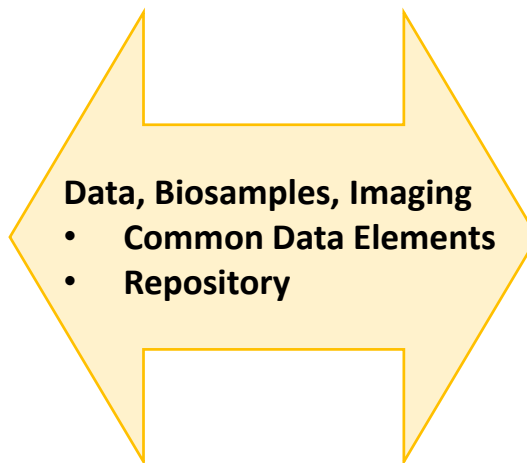


EPPIC-Net Process: Asset to Clinical Trial Protocol



EPPIC-NET Resources for other HEAL Projects

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



EPPIC-Net Process and Timing

- Awards for CCC and DCC infrastructure
 - Tentative Council approval: May 23-24
- Awards for Clinical Centers (hubs and spokes)
 - Same as above, but considering additional receipt/review dates
- OTA awards for clinical trials
 - Rolling submission; anticipate first trials in FY2020

Questions/Discussion

Pain Management Effectiveness Research Network

Jane Atkinson DDS

Director, Trial Innovation Network

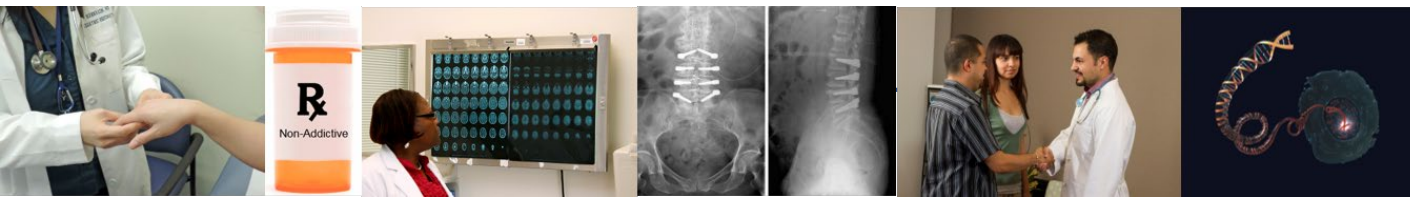
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HEAL Pain Management Effectiveness Research Network (ERN) Goals

- Compare the effectiveness of existing therapies or novel approaches for delivering current therapies to prevent and manage pain while reducing risk of addiction
- Strengthen and inform current clinical guidelines for pharmacologic and non-pharmacologic treatments for numerous acute and chronic pain conditions
- Manage acute and chronic pain in people across diverse communities
- Provide patients & practitioners with a suite of effective strategies to alleviate pain and reduce reliance on opioids
- Improve the quality of life for patients and their families



Why establish the HEAL Pain Management ERN?

- There is insufficient high quality evidence for the effectiveness of strategies currently used to manage pain (see [CDC Guideline for Prescribing Opioids for Chronic Pain](#), [AHRQ Noninvasive, Nonpharmacological Treatment for Chronic Pain - A Systematic Review](#) and [Federal Pain Research Strategy](#)).
- To rapidly respond to this national need, trials will be conducted in the HEAL Pain Management ERN, which will be established through existing infrastructure of the National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science Awards (CTSA) Program.
- This structure allows NIH to address pain management questions for multiple clinical conditions in one network.

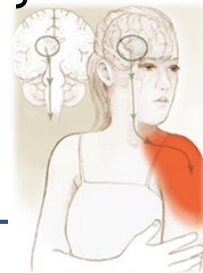
Pain Management ERN Effectiveness Trials

Definition of Effectiveness Research for the ERN

The conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, treat and manage pain conditions in “real world” settings

Interventions of interest for the ERN

Medications, biologics, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, complementary approaches, rehabilitation strategies, integrated approaches, and delivery system strategies tested in well controlled trials



HEAL Pain Management ERN Program Structure

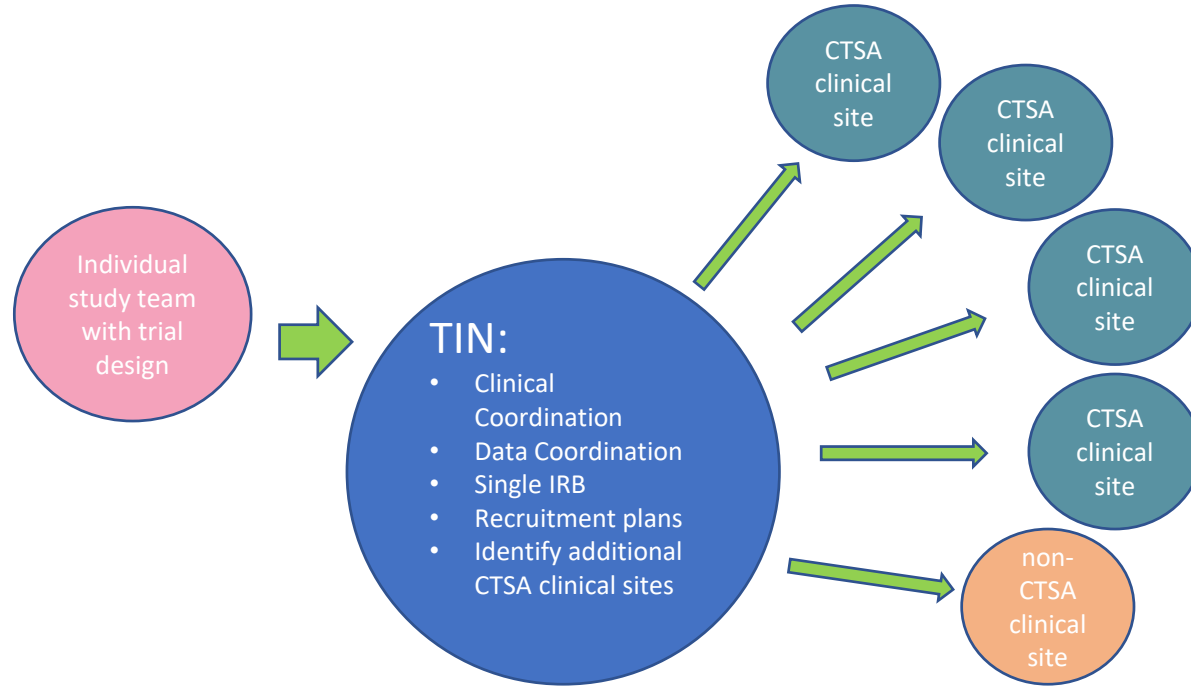
- Individual awards will support the trial study teams and costs for participants. The trials will address pain management questions across multiple NIH Institutes, Centers and Offices.
- Two additional trials will be incorporated into the ERN from existing clinical trial networks: Maternal-Fetal Medicine Units (MFMU) Network of NICHD and the NCI Community Oncology Research Program (NCORP).
- The NCATS Trial Innovation Network (TIN), an integral part of the CTSA Program, will provide clinical and biostatistical coordination and support for study recruitment. Pain experts will be included in the TIN.
- Trials will be conducted within the CTSA Program network and other clinical sites identified by the trial study teams. This allows recruitment from millions of patients with multiple pain conditions.



NCATS Trial Innovation Network will provide infrastructure including:

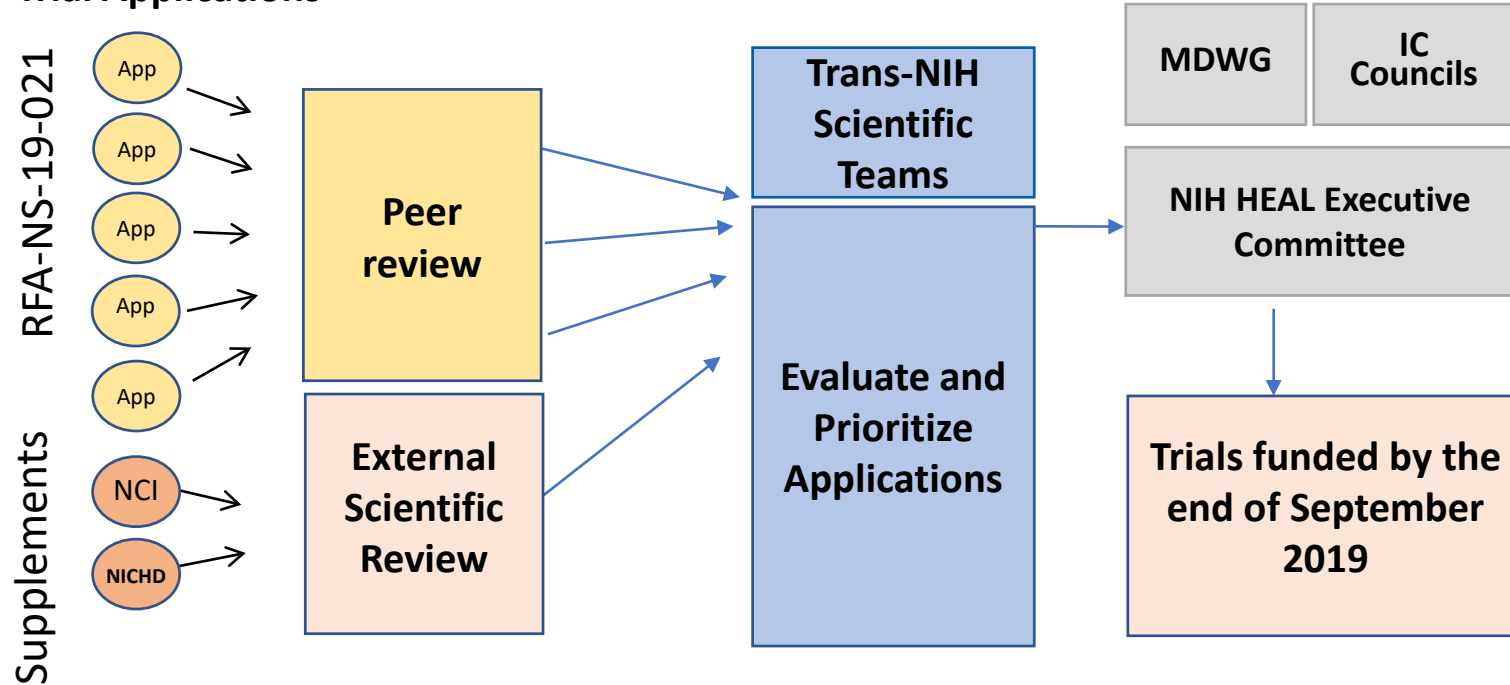
- Single IRB, Master Clinical Trial Agreements, study protocol development
- Recruitment and retention plans
- Study design, statistical analyses, data interpretation
- Manual of Procedures
- Training clinical site investigators
- Data management
- Additional site selection through the CTSA Program hubs
- Clinical operations, monitoring, project management, implementation
- DSMB reports
- Logistics for meetings

Trial study teams will work with the TIN and CTSA Hub sites



HEAL Pain Management ERN trial selection and Council review

Trial Applications



HEAL Pain Management ERN Timeline

- RFA NS-19-021 UG3/UH3 Clinical Trial Planning and Implementation soliciting individual trials:
 - HEAL Multi-Disciplinary WG Input: August, 2019
 - Anticipated council and awards: September, 2019
- Begin planning year: October, 2019
- Kick off Meeting: November, 2019

Integration of HEAL Pain Management ERN with other HEAL clinical research networks

- Regular meetings of NIH staff overseeing HEAL trials
- Standardization across networks when possible and appropriate, including use of:
 - Validated Patient Reported Outcomes (PROs)
 - Common data elements
 - Common data standards, such as CDISC
 - Common adverse events coding
- Central data repository through EPPIC-Net for future public access
- Central biospecimen storage through EPPIC-Net for future public access

Questions/Discussion