Early Phase Pain Investigation Clinical Network (EPPIC-Net)
Application and Review Webinar

March 26, 2021

NIH HEAL Initiative and Helping to End Addiction Long term are service marks of the U.S. Department of Health and Human Services.

Webinar Agenda

1:30-1:40   **HEAL Initiative: Overview and Update**

- **Rebecca Baker, PhD, Director, NIH HEAL Initiative**

1:40-1:50   **EPPIC-Net: Network Overview and Application Process**

- **Barbara I. Karp, MD, Program Director, EPPIC-Net**

1:50-2:00   **EPPIC-Net Review Process**

- **Ana Olariu PhD; Shanta Rajaram, PhD; NINDS Scientific Review Officers**

2:00-2:10   **EPPIC-Net Application via eRA Commons**

- **Laurie Roman, PhD, eRA Commons**

2:10-2:30   **Moderated Q and A**

Helping to End Addiction Long-term

Rebecca G. Baker, PhD   Director, HEAL Initiative, NIH OD

March 15, 2021

National Institutes of Health

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Crisis #1: National Overdose Deaths

- Drug overdose deaths have increased dramatically in15 years

- After a period of leveling, new increases in 2019 and 2020

- COVID-19 has had a profound impact on the ongoing opioid epidemic
  - Increased rates of drug use and overdose
  - Challenges to treatment, patients and communities

> 20% increase
10% to 19% increase
0% to 9% increase
decrease
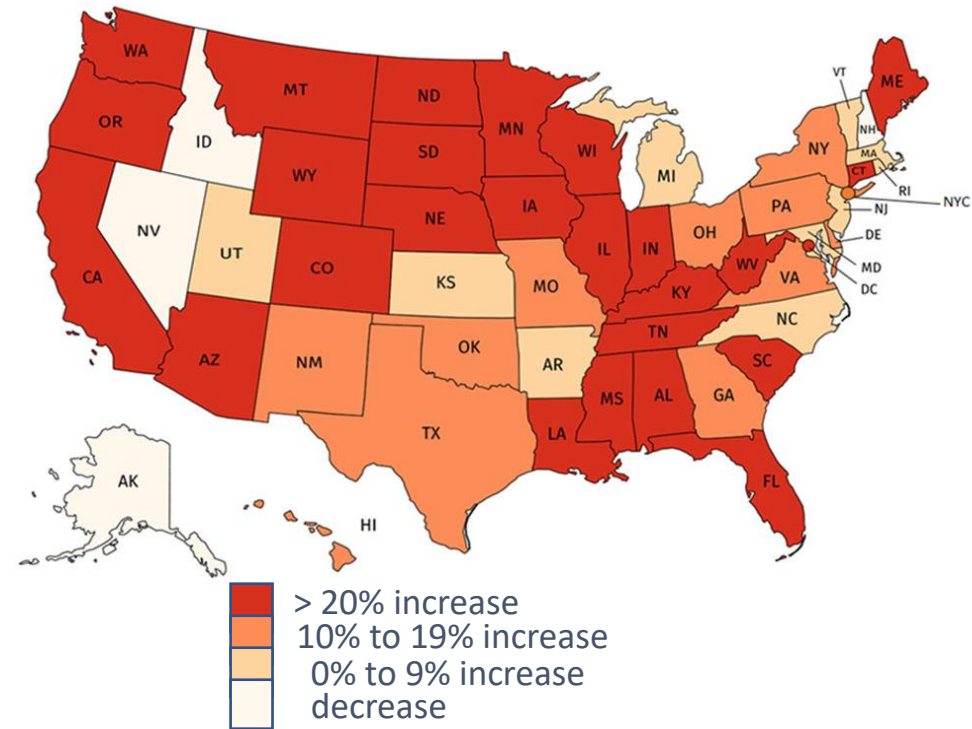
Percentage change in 12-months on all fatal drug overdoses ending May 2020

National Public Health Emergency declared in 2017

Crisis #2: Chronic Pain in the U.S.

- o 50 million adults are affected by chronic pain
- o 25 million report severe pain on a daily basis
- o 20 million have high impact chronic pain

CDC, Morbidity and Mortality Weekly Report, Sept. 2018

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The Response:
$500 million/year Sustained Research Investment

25+ HEAL Research Programs

Prevention – Basic & Translational Research – Clinical Trials – Implementation Science
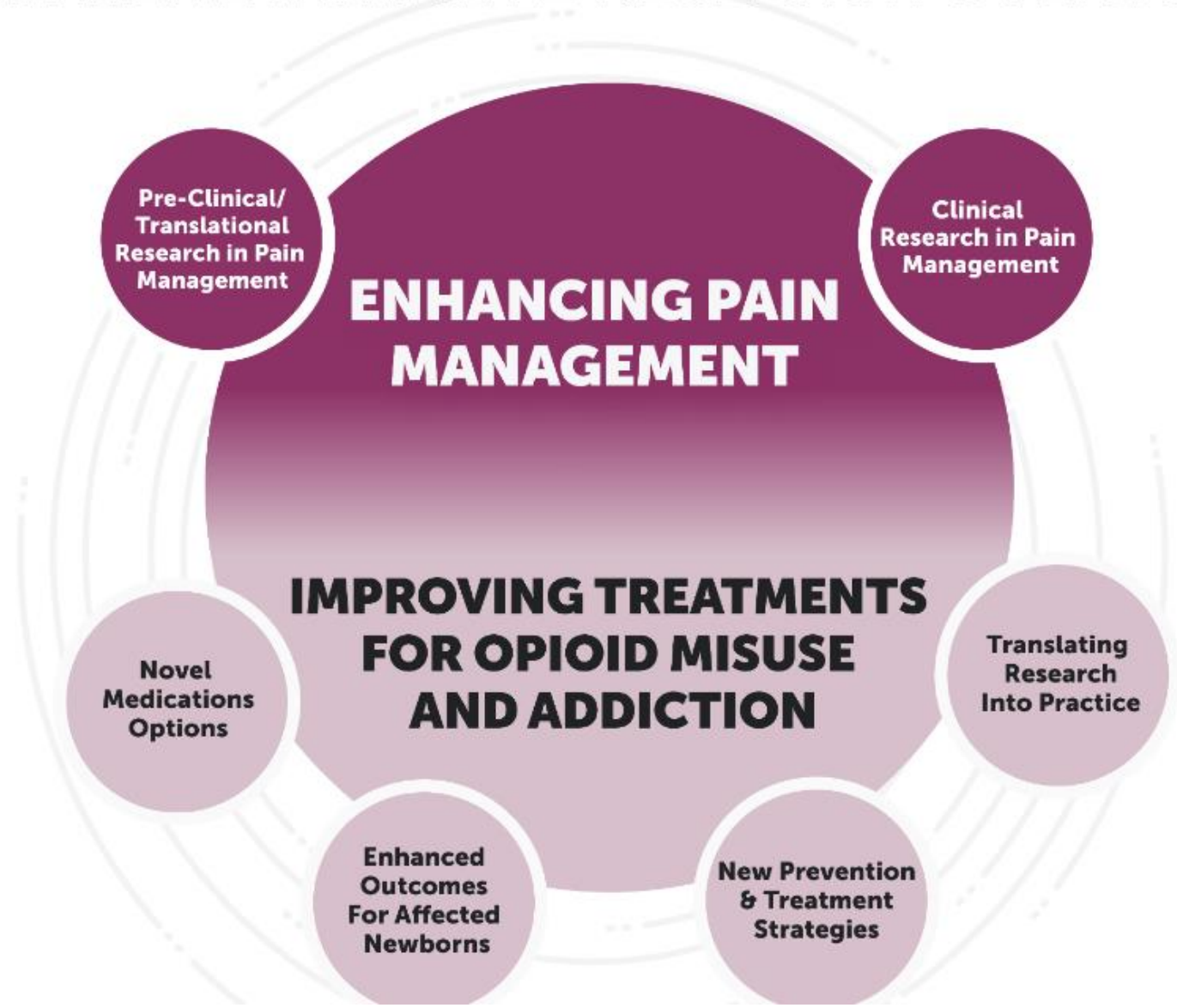
12 NIH ICs leading studies

Trans-NIH governance structure

Partnerships across government, communities, and the private sector

NIH · Helping to End Addiction Long-term
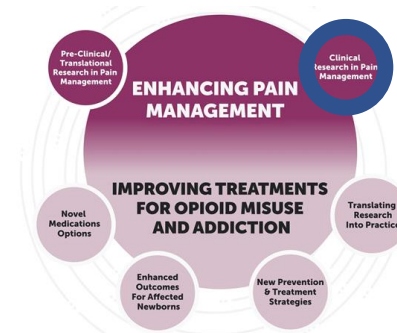
Clinical Research in Pain Management

- **Early Phase Preclinical Investigation Network (EPPIC Net)**
  - 14 grants for infrastructure; NINDS led
  - Trial under development for CCR2 antagonist for knee osteoarthritis pain

- **Back Pain Consortium**
  - 14 research projects; NIAMS led
  - 3 mechanistic research centers, 7 technology sites, 2 phase II trials, data center, and 1 supplement to study back pain in the context of OUD

- **Hemodialysis Opioid Prescription Effort (HOPE)**
  - 8 clinical sites, data center; NIDDK led
  - Test non-pharmacological interventions and buprenorphine for pain in patients in kidney dialysis

Clinical Research in Pain Management

- **Pain Effectiveness Research Network (ERN):**
  - 8 projects; NCATS infrastructure with NICHD, NIA, NIAMS, NIDA, NINR, NCI trials
  - Pain conditions studied: knee osteoarthritis, postsurgical pain in adolescents, post-mastectomy pain, acute pain post cesarean, chronic pain in cancer survivors, chronic pain in veterans with OUD

- **Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing (PRISM):**
  - 7 projects; NCCIH NIA, NIAMS, NINR
  - Nonpharmacological management of diffuse fibromyalgia pain, post-surgery, sickle cell and chronic low back pain

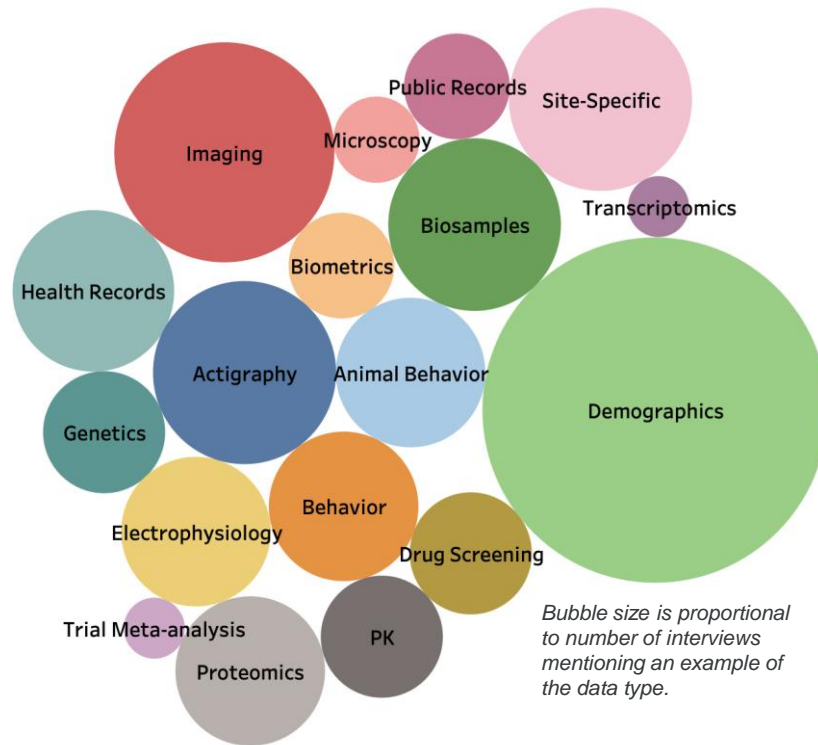# Clinical Research in Pain Management Accomplishments

- Data harmonization through a set of pain-unique Common Data Elements for HEAL clinical pain studies

- Iterative model to inform precision medicine for chronic low back pain
  - Multiple contributions to chronic low back pain and treatment interventions — from anxiety to tissue damage and from psychotherapy to surgery

- FDA IND for use of buprenorphine for pain management as part of multidisciplinary pain management for patients on dialysis for end stage renal disease

Cross-cutting HEAL themes

- Sharing and open access of data
  - HEAL Public Access and Data Sharing Policy
  - Secure infrastructure for making HEAL data FAIR
  - Harmonized measures established by HEAL teams

- Engagement of research participants, patients, and stakeholders

- Importance of partnerships, diversity and inclusion in HEAL research studies

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HEAL Data Ecosystem

Bubble size is proportional to number of interviews mentioning an example of the data type.

- Enable access of HEAL data for various stakeholders through a user-friendly web portal
- Foster secondary research and new discoveries
- Maximize access to and use of data analysis tools and resources
- Provide sustainability of HEAL digital assets beyond individual awarded programs

"We are committed to making data from this investment rapidly available for use by policymakers, patients, and clinicians and importantly, to other scientists within and outside of HEAL to promote new discovery"

Use Cases: Engagement with the HEAL Data Platform

As a **community-based service organization** we want to **support people misusing opioids in our communities** in order to **save lives and reduce suffering.**

As a **clinician treating patients with chronic pain,** I want **access to the latest pain research and clinical trial results** to **identify and track potential new approaches to assist my patients.**

As a **research expert in opioid misuse and addiction,** I want to **compare different psychosocial interventions** to **optimize medication-based treatment approaches** for opioid use disorder.

As a **pain translational researcher,** I want to **validate a pain drug target in multiple species** in order to **have a complete evaluation of a possible novel pain drug target.**

www.heal.nih.gov

EPPIC-Net Goal

Reduce reliance on opioids by accelerating early-phase clinical trials of non-addictive pain therapeutics ("assets"), including drugs, small molecules, biologics and devices (NOT-NS-19-043)

EPPIC-Net provides

- Phase 2 clinical trials for accepted assets from Industry and Academia. Assets can be novel or re-purposed. Must be phase 2 ready (with IND/IDE or IND/IDE ready)
- Proposal should focus on specific pain population/condition with high unmet need
- Proof-of-concept testing/validation of biomarkers
- Well-characterized adult and pediatric pain patient cohorts
- Incorporation of deep phenotyping into trials
- Innovative study design
- Continuous learning from experience to engineer adaptive, ever-improving early-phase testing of new pain therapies

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EPPIC-Net Infrastructure
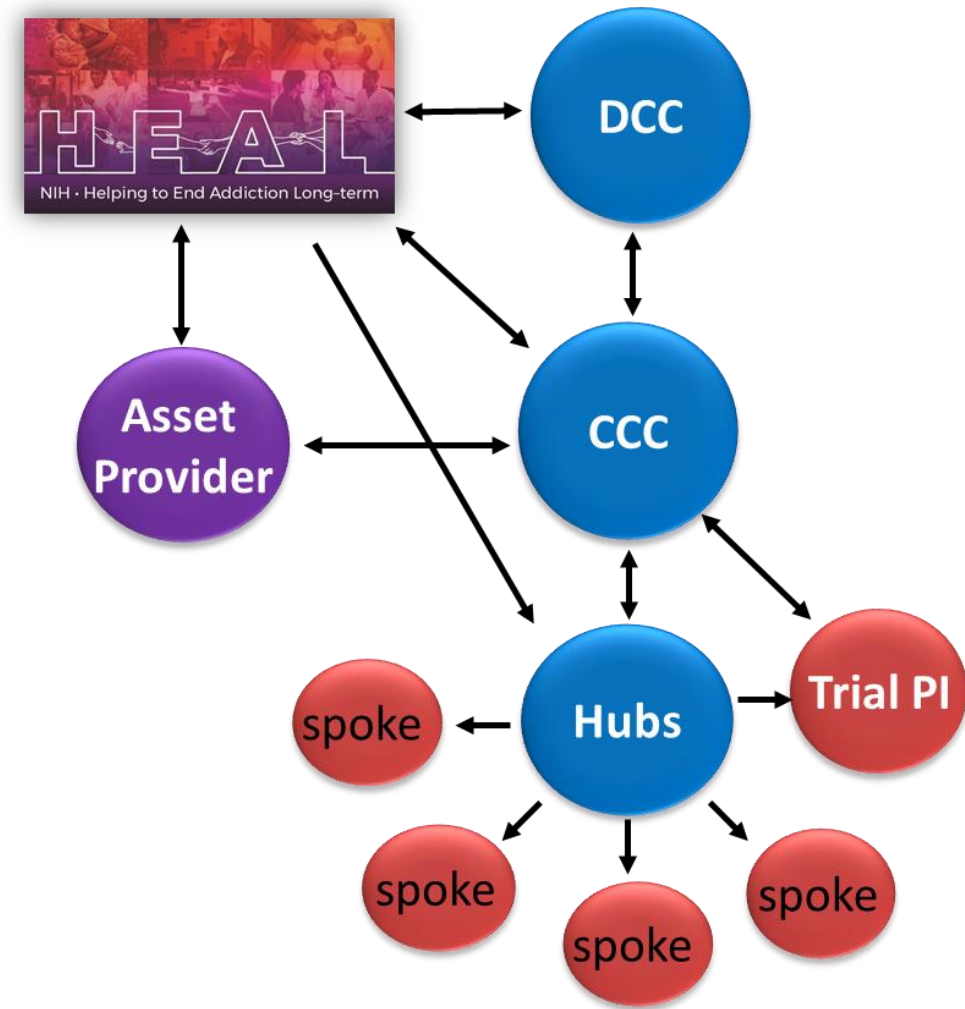
NIH/HEAL/NINDS: interacts with all EPPIC-Net components, provides guidance/oversight of budget and milestones
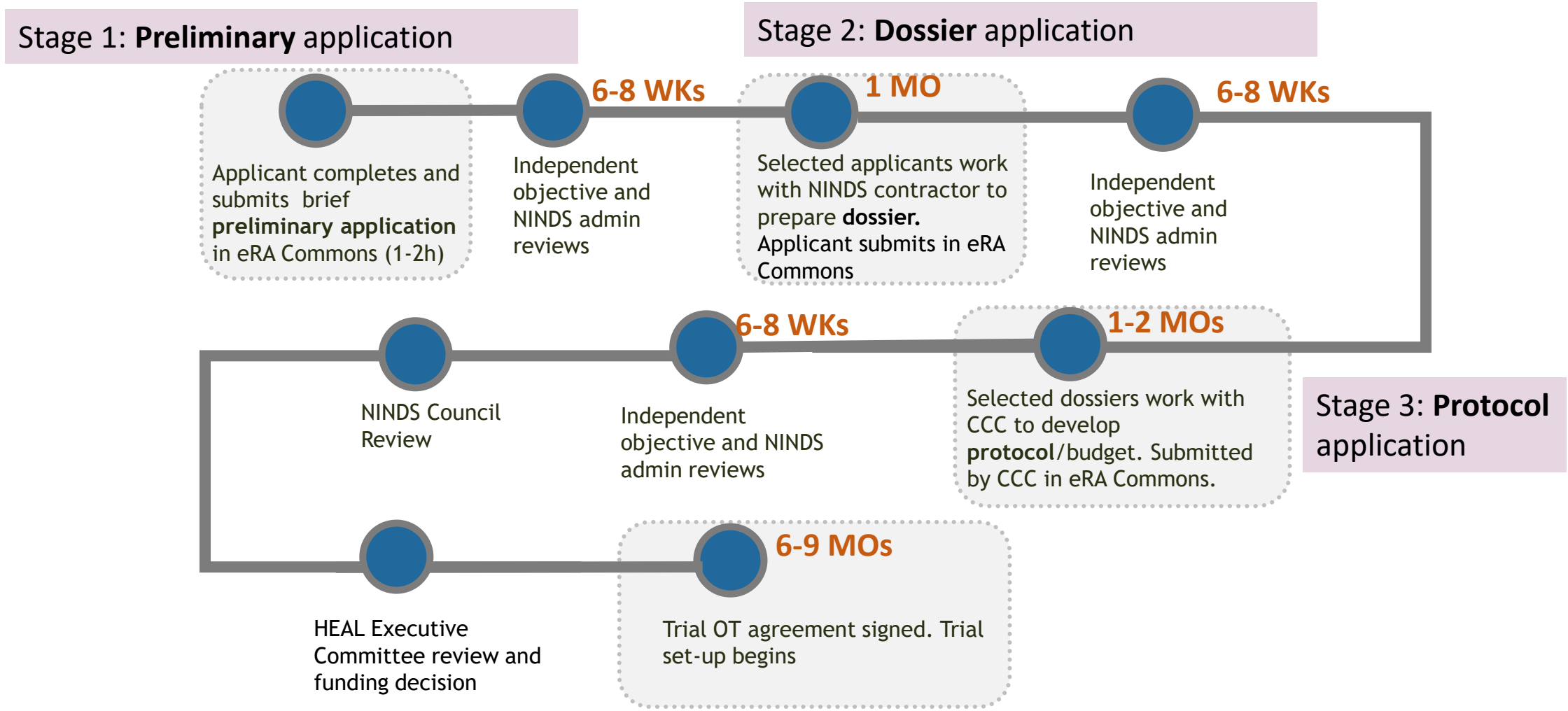
Asset Provider: provides the pain therapeutic (drugs/device etc.) for study; **retains IP/property rights to asset**

Clinical Coordinating Center: (MGH) develops protocol in collaboration with asset provider, matches hubs/spokes to protocol/asset, oversees trial conduct, distributes and manages trial funds.

DCC: (NYU) receives and centralizes data, provides statistical input and analyses, harmonizes data, provides reports to regulatory agencies, manages EPPIC-Net biorepository

Clinical Hubs/Spokes: (see EPPIC-Net website for listing) identify trial investigators, recruit and enroll participants, conduct the trial study procedures, collect and report data to DCC and CCC

EPPIC NET Application & Review Process

Stage 1: **Preliminary** application

Stage 2: **Dossier** application

6-8 WKs

Applicant completes and submits brief **preliminary application** in eRA Commons (1-2h)

Independent objective and NINDS admin reviews

1 MO

Selected applicants work with NINDS contractor to prepare **dossier.** Applicant submits in eRA Commons

6-8 WKs

Independent objective and NINDS admin reviews

6-8 WKs

NINDS Council Review

Independent objective and NINDS admin reviews

1-2 MOs

Selected dossiers work with CCC to develop **protocol**/budget. Submitted by CCC in eRA Commons.

Stage 3: **Protocol** application

HEAL Executive Committee review and funding decision

6-9 MOs

Trial OT agreement signed. Trial set-up begins

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Application process: preliminary application

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

https://heal.nih.gov/research/clinical-research/eppic-net

PLEASE NOTE: EPPIC-NET IS OPEN TO APPLICATIONS
Download the Preliminary Application Packet (PDF, 3MB) ***Updated application packet posted on February 25th, 2021. Please utilize the updated application form and instructions***
USE ROA #OTA-21-005 (PDF, 180KB) TO SUBMIT YOUR APPLICATION IN eRA COMMONS
Updated ROA published on February 25th, 2021. Please utilize this number when submitting preliminary applications
Please Note: Preliminary applications are accepted at any time and reviewed on a rolling basis.

Detailed information regarding the EPPIC-Net application and review process is available below.

The **preliminary application packet** is available on the EPPIC-Net and HEAL websites
1. EPPIC-Net and application overview
2. EPPIC-Net preliminary application (fillable pdf)
3. Line-by-line instructions for preliminary application
4. eRA Commons Instructions

POTENTIAL APPLICANTS ARE STRONGLY ENCOURAGED TO TALK TO US BEFORE SUBMITTING AN APPLICATION

The preliminary application asks only for high level information
- Asset identification, class, mechanism of action
- Brief citation of pre-clinical and clinical studies supporting asset
- Known safety concerns
- Proposed indication, dose/exposure, route of administration
- What makes asset unique/better than others in class or for indication
- Freedom-to-operate letter from asset owner

Common reasons for prelim application failure to move forward
- ❖ Asset not phase-2 ready
- ❖ No clear advantage over available therapeutics in same class
- ❖ Weak scientific basis
- ❖ Safety concerns

Application process: dossier application

Selected applications work with an NINDS contractor to prepare the Stage 2/Dossier application

<u>Dossier sections</u>
Summary
Scientific Rationale and Unmet need
Asset Biology, Pharmacology, and/or Physiology
Target Product Profile
Non-clinical Data (pharmacokinetics, safety
     pharmacology
Toxicology Summary
Prior Clinical Experience
Asset Preparation for clinical trial
Competitive Analysis
Additional Considerations (e.g. need for EPPIC-Net in asset development)

<u>Applicant role in dossier development</u>
Provide contractor with detailed
     information to support dossier.
Provide FDA filings, IB
Address prelim application reviewer
     concerns in dossier
Submit dossier in eRA Commons

Contractor protects confidentiality
Timeline: 3 working weeks

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Application process: Protocol Application

Selected applicants work collaboratively with the EPPIC-Net CCC (and DCC) to prepare the trial protocol & budget

- A Protocol Principal Investigator with appropriate expertise for asset/condition is chosen from EPPIC-Net investigators
- Study population finalized
- Trial design may be novel; may incorporate placebo and active controls
- May incorporate biomarker evaluation/validation
- Role of applicant in trial defined
- Budget and timeline developed

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Funding

> ## "Other Transaction" Awards are used to fund EPPIC-Net Clinical Trials
> *OT award is made to CCC for distribution for trial conduct. *The asset owner does not receive funds.*

Successful applicants receive access to EPPIC-Net for the development and completion of the asset clinical trial. Data from the clinical trial can be used to support further therapeutic development and later phase trials.

The Asset Holder/Applicant is expected to provide the therapeutic asset for the clinical trial. The Asset owner retains intellectual property rights.

EPPIC-Net is open U.S. and non-U.S. applicants

EN20-01: A 24-week Week Study to Evaluate the Safety and Efficacy of CNTX-6970 in Subjects with Moderate to Severe Knee Osteoarthritis Pain

Study Design: Randomized, allocation concealed, multicenter, placebo-controlled, multi-crossover: 150 patients; randomized 1:1:1

Randomized treatment allocation

Randomized order allocation

CNTX 100mg bid/placebo

CNTX 300mg bid/placebo

Celecoxib 100mg bid/placebo

Each allocation group is randomized further into two 12-week blocks with different drug/placebo order
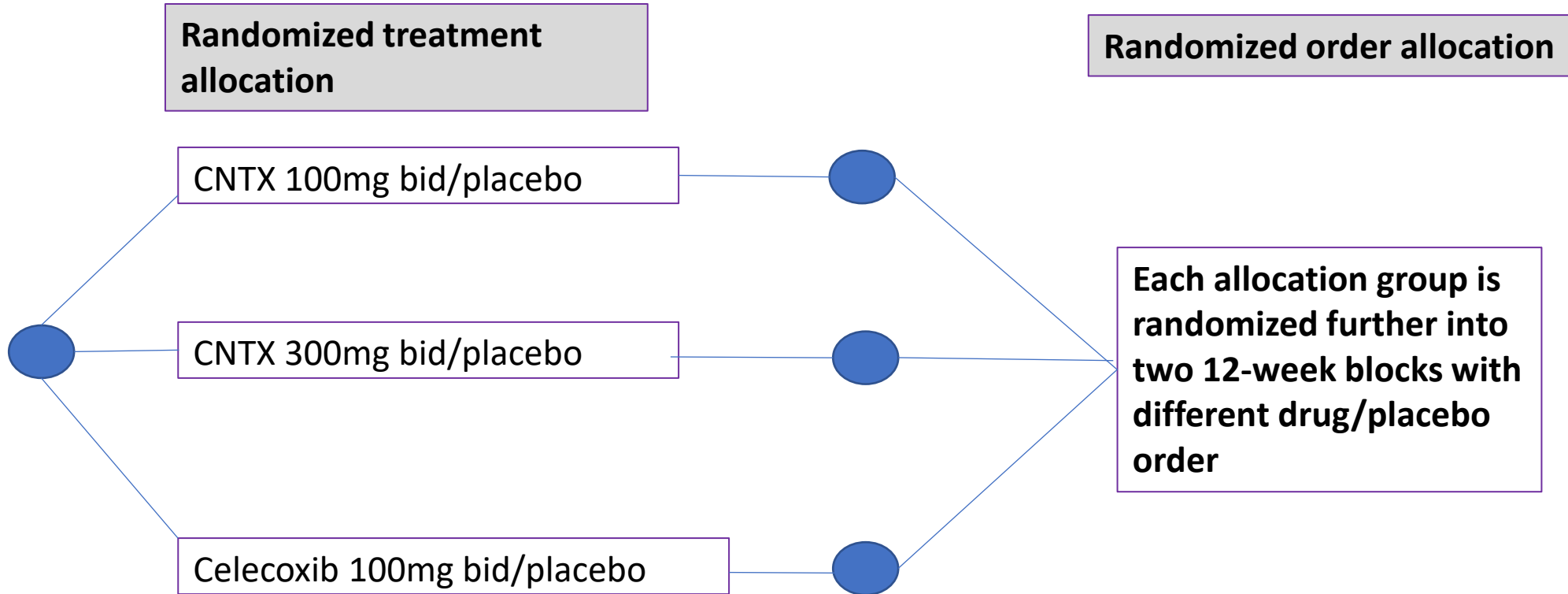
EPPIC-Net Staff Contacts

EppicNet@ninds.nih.gov

- **Barbara I. Karp- karpb@ninds.nih.gov**
- **Rebecca Hommer- rebecca.hommer@nih.gov**
- **Jennifer Beierlein- jennifer.beierlein@nih.gov**
- **Marlene Peters-Lawrence – marlene.peterslawrence@nih.gov**

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EPPIC-Net
Review Process Update

3/26/2021 **Ana Olariu, PhD; Shanta Rajaram, PhD.**

Independent/Objective Review

Independent/Objective Reviews are **NOT**

standard NIH Peer Reviews!!

EPPIC-Net Review process

	WHAT:	WHO:	AWARD:
Stage 1	Preliminary Application (brief asset data)	Asset applicant	NO
Stage 2	Dossier Application (in depth asset data)	Asset applicant working with NINDS Contractor	NO
Stage 3	Clinical Trial Protocol	EPPIC-Net CCC (with DCC, Hub PIs and Applicant)	YES

Independent/Objective Review Panel
Evaluates assets based on template, full dossier, and clinical protocol

NIH IC Staff

HEAL MDWG   **NINDS Council**

NIH HEAL Executive Committee
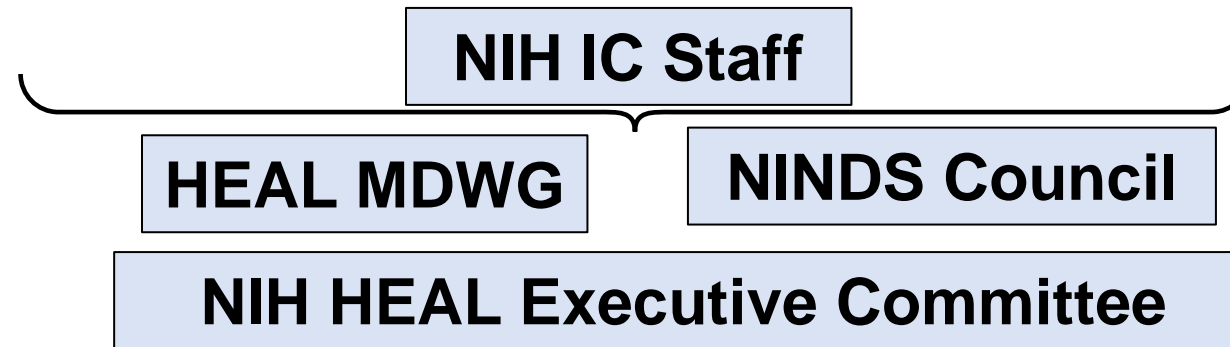
EPPIC-NET Application Submission and Review Process
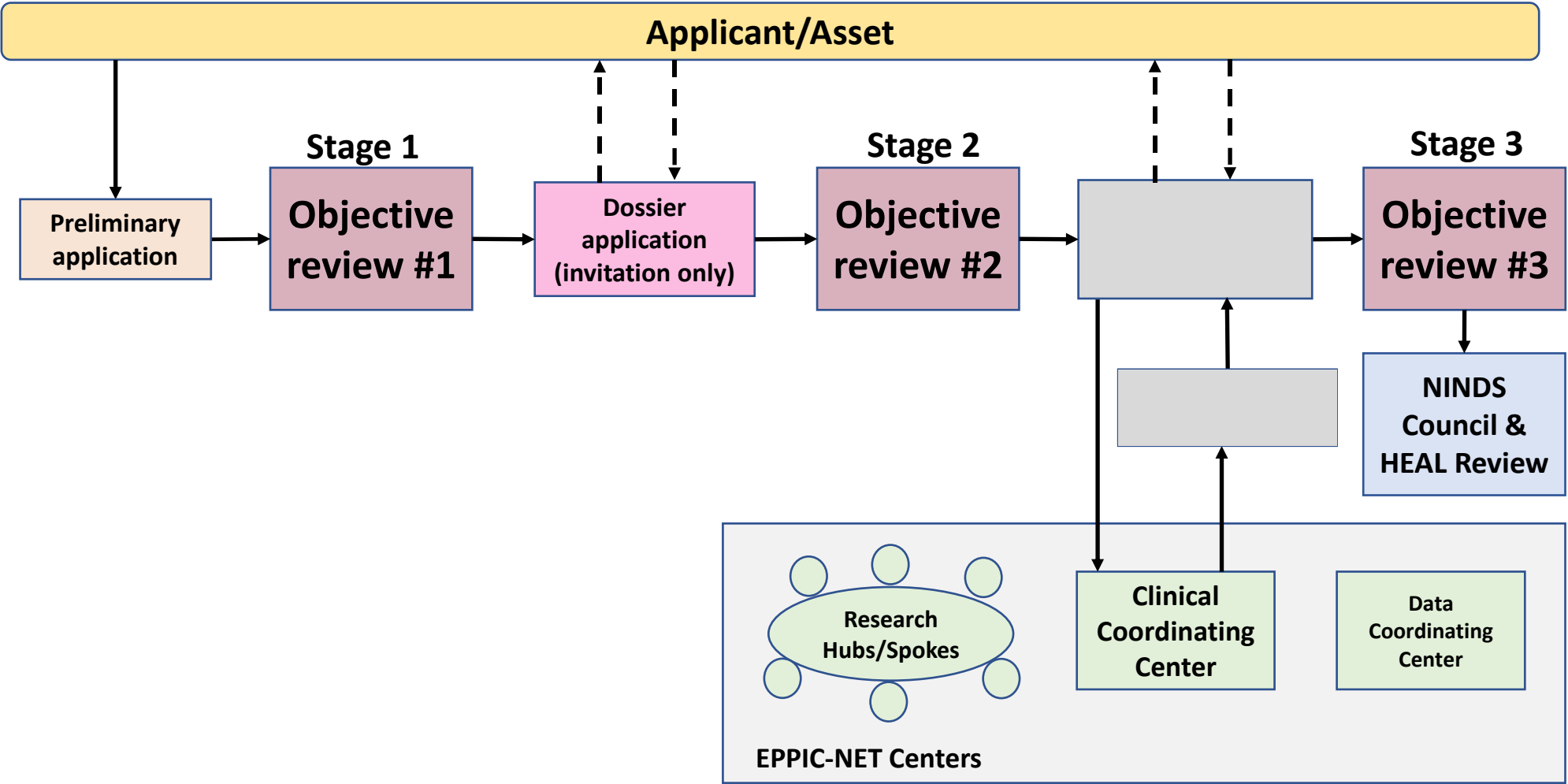
Goals of Independent/Objective Review

- To have a fast, fair streamlined review process.
- To get input from the outside experts for NINDS/HEAL consideration of EPPIC-NET awards.
- Obtain reviewers' *individual opinions* on each proposed therapeutic
  - Consensus is NOT the goal.
- Conflicts of Interest (COI) will be managed using principles of NIH review COI policy, as a guide.

Independent/Objective Review Panel

- 20-30 Core panel members. Same Panel reviews EPPIC-NET applications at each application stage, although not all members are present at every meeting.

- Expert *ad hoc* reviewers with special expertise are added at each stage as needed to cover science, rigor, and methodology.

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Application submission and Independent/Objective Review process

- Preliminary applications (Stage 1) are submitted on a rolling basis.
  - Meeting cut-off dates are posted on the EPPIC-NET webpage

- Dossier (Stage 2) and Clinical Protocol (Stage 3) applications are submitted by invitation only and are submitted in eRA Commons under different ROA numbers.

- EPPIC-Net reviews are conducted on a rolling basis determined by the number and timing of application submissions.

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Stages 1, 2 and 3: Independent/Objective Review

Different review criteria matched to stage of review.

- **Stage 1 (preliminary application)** – High level evaluation. Focus on the asset suitability for EPPIC-NET with consideration of target population. Less emphasis on proposed trial design.

- **Stages 2 (dossier application)** – Emphasis on drug/biologic asset pharmacology or asset device specifications and pre-clinical/clinical data in support of the asset for the proposed population. Early consideration of proposed clinical trial design.

- **Stage 3 (protocol application)** – Thorough review of all aspects of the clinical trial. Review also includes consideration of criteria such as Protection of Human Subjects, safety monitoring, and Inclusion plans (gender, minorities, and individuals across life span).

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Application Review Outcome

- Pre-meeting individual reviewer' assessment will identify key strengths and weaknesses and an initial recommendation for a color "Bin".

GREEN – Meritorius
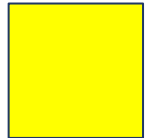
YELLOW – Meritorius but some concerns noted
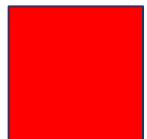
RED – Not deemed meritorious, serious concerns noted; may *NOT* be discussed

Post-Objective Review process/Funding decisions

- Post-Independent/Objective review, the NINDS convenes an internal administrative review committee consisting of NINDS program officers knowledgeable about pain and clinical trials.

- NINDS EPPIC-NET staff will notify the applicants of selection decisions and decision-driving concerns. Review Summary Statements are **NOT** provided to applicants.

- The final decision for funding a *Clinical Protocol application (Stage 3)* lies with the NINDS Director with NINDS Council considerations and HEAL leadership.

EPPIC-Net: Preparation, Submission & Tracking in eRA Commons

Laura M. Roman, MBA, PhD

eRA Commons

- Submitting organization must be registered at eRA Commons
- Streamlined Commons registration process: no DUNS required for submission
- Organization much have an individual with role of Signing Official
- PD/PI must have Commons ID and be affiliated with submitting organization
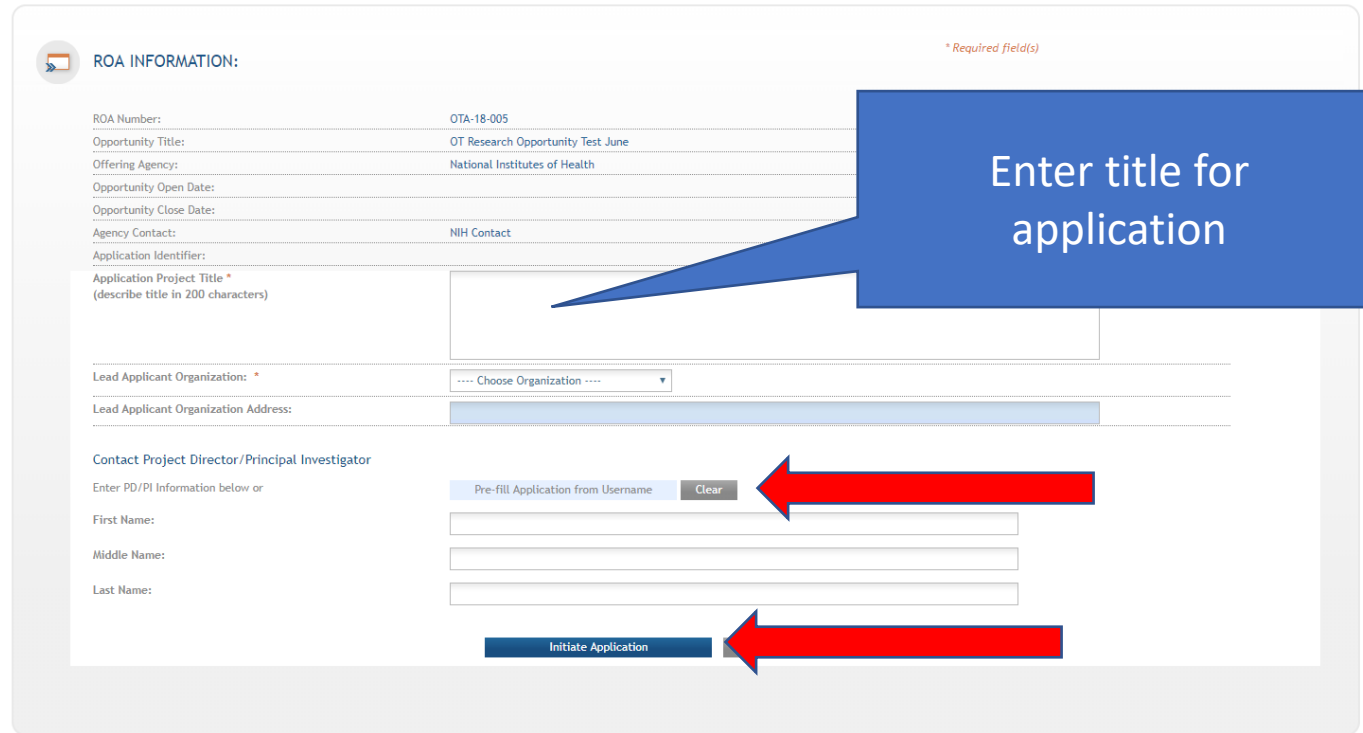
Application Preparation & Submission in ASSIST

- ASSIST is NIH's System to System solution
- Application preparation, submission & tracking in a single system
- Streamlined submission- single form + attachments
- Use opportunity provided in EPPIC-Net (OTA-21-005) in this format
- If PI completes profile in eRA commons, can use Commons ID to prepopulate select fields in the application

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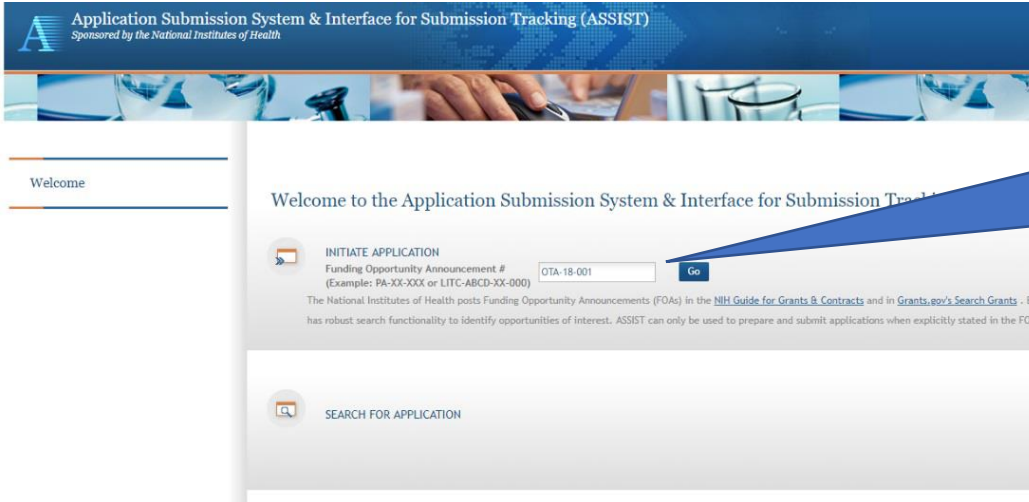
ASSIST

Enter opportunity announcement "OTA-21-005" (no quotes) here

Enter title for application

Users can access ASSIST through eRA Commons or directly using https://public.era.nih.gov/assist or searching for NIH ASSIST from your browser

eRA Commons

Unique identifier for application

eRA Commons

Complete information for organization, PI and business officials

Fields with * are required

Save and keep locked prevents someone else from working on the form at the same time. Save and release lock, returns form to status where it can be edited by someone else.

eRA Commons

◂ Hide Navigation

Actions ❓

- RETURN TO APPLICATION
- MANAGE ACCESS
- PREVIEW CURRENT FORM
- VALIDATE APPLICATION
- VIEW STATUS HISTORY
- UPDATE SUBMISSION STATUS
- COPY APPLICATION
- DELETE APPLICATION
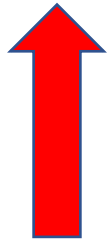
Application Information ❓

| Summary | **OTA Core** |

NIH Other Transaction Applic...
OTA Core v1.0 ❓

Edit

Submission Type

Application Information

Application Identifier:	21115
Application Project Title:	Clinical Center for All of Us NIH Program
PD/PI Name:	AARONS, GREGORY
Organization:	
Project Period:	
Status:	Ready for Submission **Submit Application**
	Submit Application
Status Date:	2018-05-16 10:50:09.000 PM EDT

Only individuals with signing official role can submit
The system will validate the application
Errors must be corrected

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eRA Commons

Clicking accession number (in red circle) will take the user to eRA Commons to view assembled application image.

Application Information ⓘ

> ⓘ OTA Application has been submitted, email notifications will be sent when application is processed. Also you may use the Check Submission Status feature in ASSIST to get the up-to-date status of the submitted application.

Summary | OTA Core

Application Information

Application Identifier:	32933
Application Project Title:	NINDS Demo applicationv2
PD/PI Name:	Abelà, Aléxändér Müller
Organization:	UNIVERSITY OF CALIFORNIA, SAN DIEGO
Project Period:	03/01/2022 - 09/01/2024
Status:	Submitted View Submission Status Details
Status Date:	2019-03-26 11:40:21.000 AM EDT

ASSIST

Submission Date:	2019-04-01 10:28:06 AM
Submitting AOR:	ROMANL_SO
ASSIST Submission Status:	Submitted
Submission Status Date:	2019-04-01 10:28:06 AM

Agency

View Agency Submission Errors and Warnings

Agency Tracking #:	4271519 (To View Commons Status and Application Details) To View Commons Post Submission Actions
Agency Status:	PROCESSED
Agency Status Date:	2019-04-01 10:28:11 AM

Close

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Application for OTA Award

TYPE OF SUBMISSION	Prior Submission Tracking Number
○ Corrected Submission	

1. APPLICANT INFORMATION

Organization Name*: UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
Department:
Division:
Street1*: UNIVERSITY OF TEXAS HLTH SCI CTR
Street2: 7000 FANNIN STREET, UCT 1000
City*: HOUSTON
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 770305400

2. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)

- Bookmarks and TOC
- Separate attachment fields identified by file names
- Communications to applicants regarding status

**NIH Other Transaction Application
Table Of Contents**

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Q&A

Please submit your questions in the Q&A box

Thank You!

This webinar will be posted on the EPPIC-Net Program page.

Please contact EPPICNet@ninds.nih.gov with further questions.

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