NIH HEAL INITIATIVE

Non-addictive Analgesic Therapeutics Development

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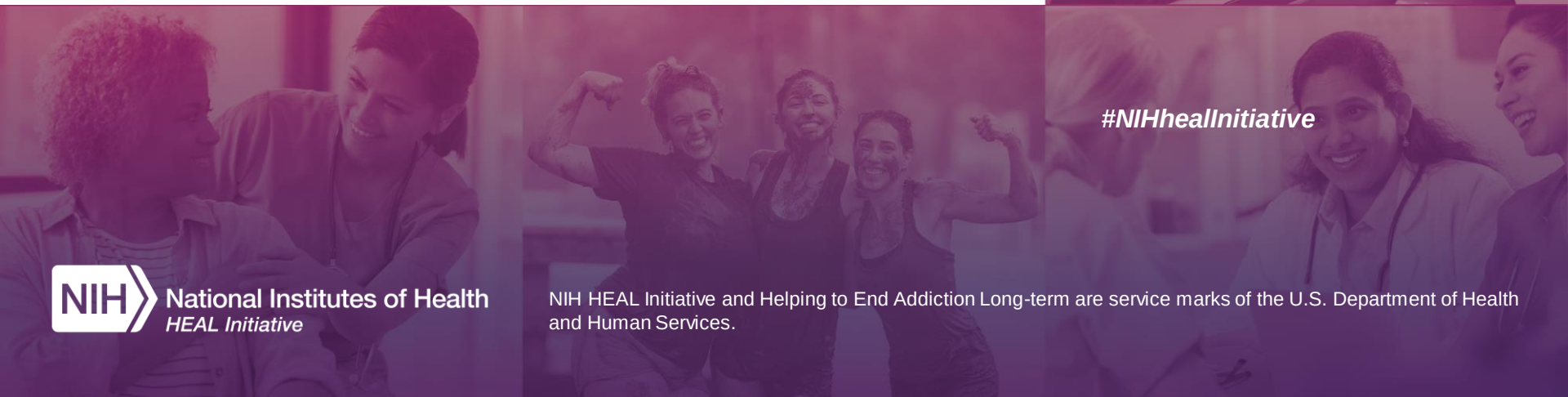


#NIHhealInitiative

National Institutes of Health
HEAL Initiative

NIH Helping to End Addiction Long-term (HEAL) Initiative: Pain Research Priorities

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
- Inform best practices for effective pain management while minimizing risk of addiction

Read about the research plan:

www.nih.gov/heal-initiative


JAMA June 12, 2018 Opinion

VIEWPOINT

Helping to End Addiction Over the Long-term
The Research Plan for the NIH HEAL Initiative

Collins, Koroshetz, Volkow; JAMA, 2018

Federal Pain Research Strategy 2017

strategic plan for pain research across federal agencies

PREVENTION OF ACUTE & CHRONIC PAIN

ACUTE PAIN & ACUTE PAIN MANAGEMENT

TRANSITION FROM ACUTE TO CHRONIC PAIN

CHRONIC PAIN & CHRONIC PAIN MANAGEMENT

DISPARITIES

WHAT HAPPENS AND TO WHOM?

WHY AND HOW DOES IT HAPPEN?

HOW TO MANAGE?

BASIC SCIENCE

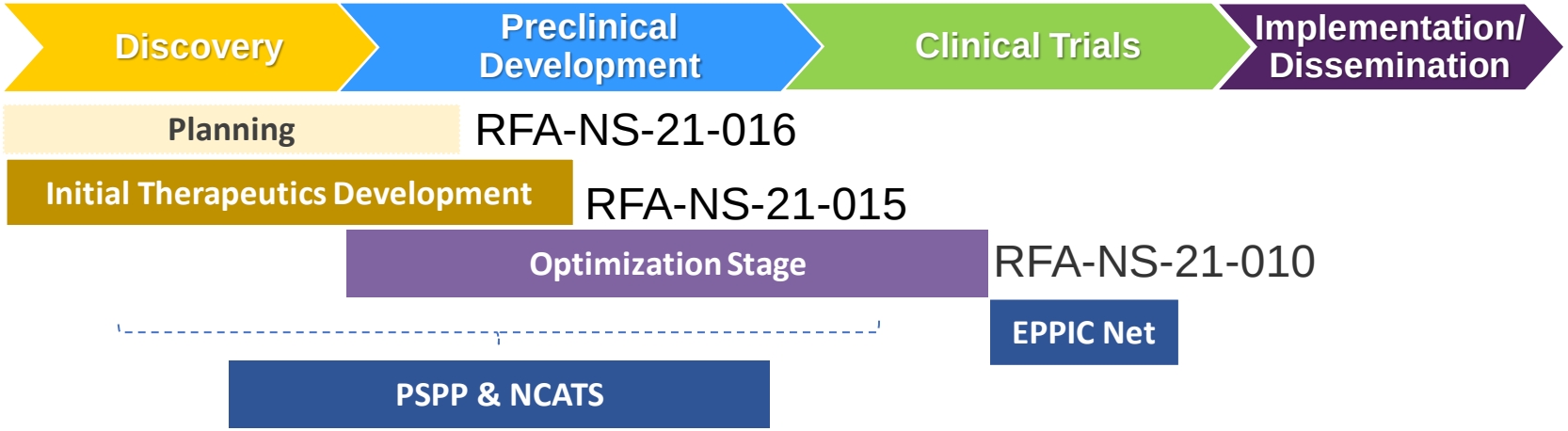
CLINICAL SCIENCE

UNDERSTAND MECHANISMS

TRANSLATE/ TREAT

https://iprcc.nih.gov/sites/default/files/iprcc/FPRS_Research_Recommendations_Final_508C.pdf

Proposed HEAL Analgesic Development Program

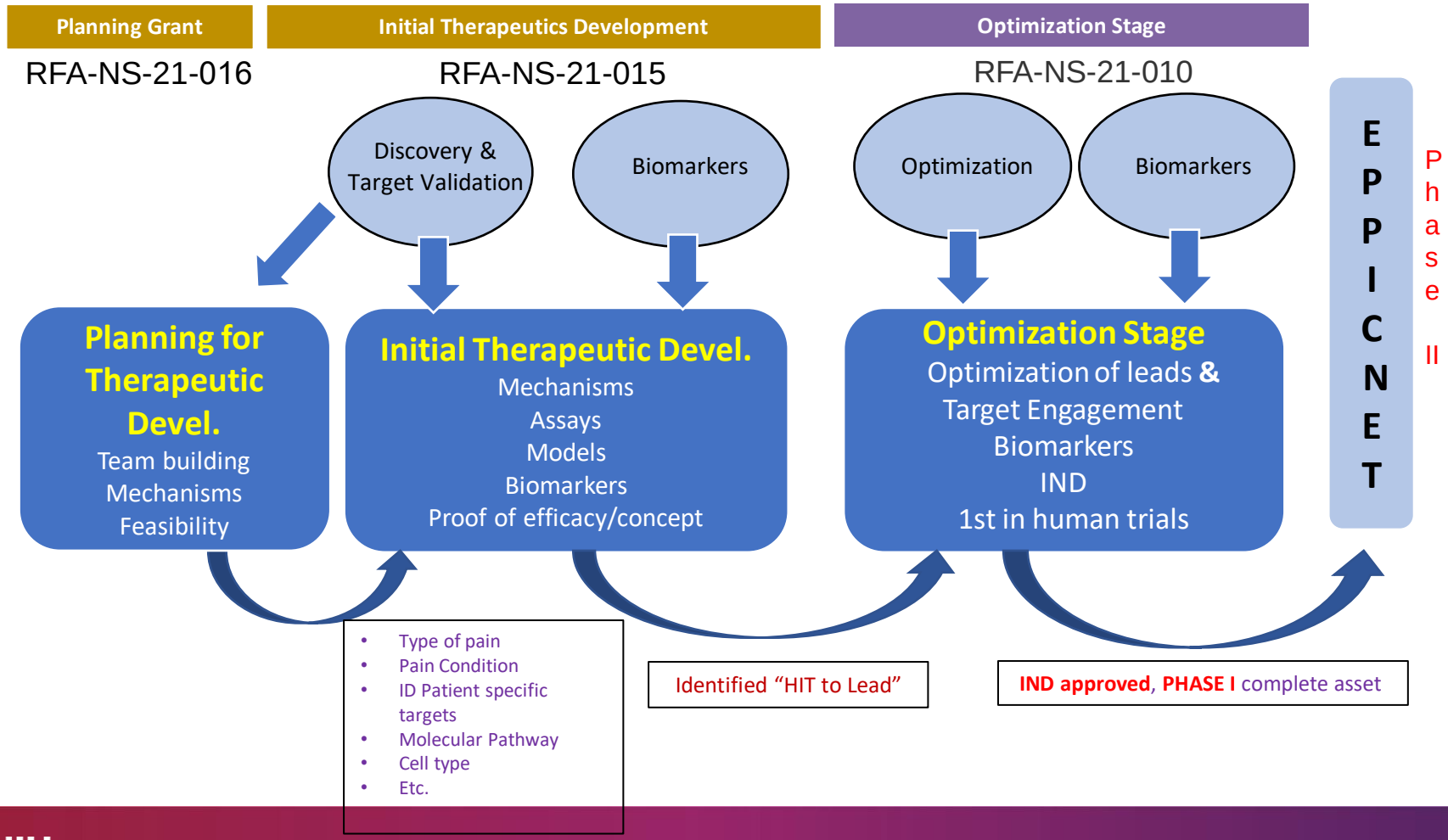


Analgesics Development:

- ✓ Focus on deliverables
- ✓ Focus on scientific challenges
- ✓ Reduce program complexity
- ✓ Incentivize industry to reinvest

Grants | Grants & Contracts | Grants, Contracts & Intramural Resources

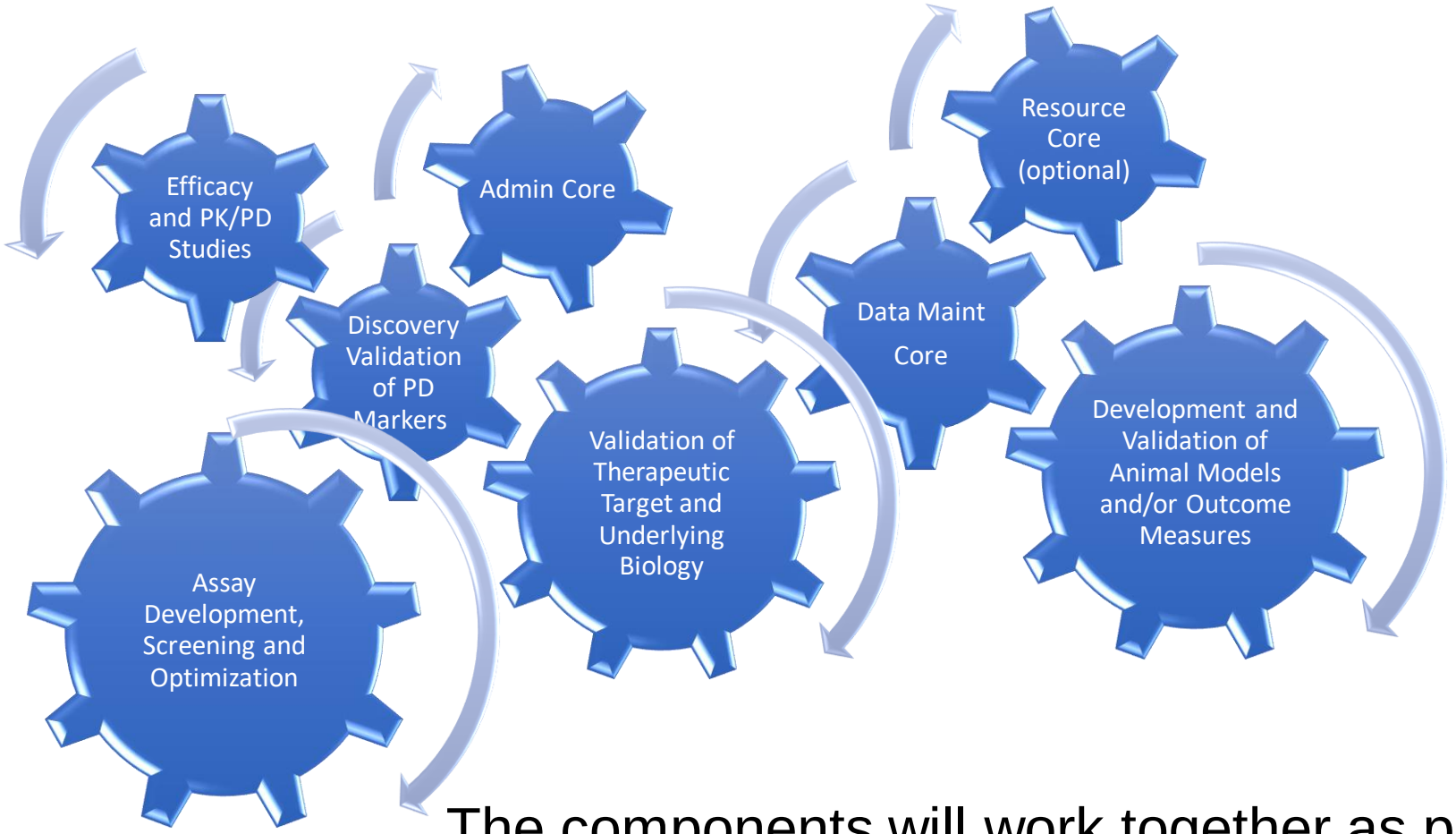
HEAL Analgesic Development Program



Planning R34 v Team U19

- U19 Entry Criteria:
  - Multidisciplinary team
    - evidence it has expertise AND can work together
  - Biological rationale - Feasibility
    - preliminary data
    - literature-based evidence
- U19 is up to 5 years (if milestones are met)
  - direct costs of $1.5 million per year including all consortium and subaward costs
- R34 is 2 years
  - may not exceed $500,000 per year, including consortium costs
  - Build multidisciplinary team
  - Preliminary data – Biological Rational - Feasibility

U19 Team Research for Initial Translational Efforts



The components will work together as part of a whole project to develop a single asset.

U19 - Initial Therapeutic Development

- Support research program of multiple projects
  - specific major objective or program goal
  - multidisciplinary approach
- Cooperative agreement
  - organized efforts of large groups
  - Federal programmatic staff involvement
    - assist investigators
    - terms and conditions of award. investigators have primary authorities and responsibilities
- Each research project
  - leadership by established PI representing special competencies
  - Each project has **unity and interdependence** directly related total research effort
- Can provide support for shared resources

U19 – Components

- Overall Integrated Development Plan: required; 12pg
- Administrative Core: required; 1pg
- Data Management Core: required; 1pg
- Resource Core: optional; 3pg
- Research Components: required; # min. 3; max. 5
  - Validation of Therapeutic Target and Underlying Biology
  - Development and Validation of Animal Models and/or Outcome Measures
  - Assay Development, Screening and Early Optimization
  - Discovery and/or Validation of Pharmacodynamic Markers
  - Efficacy and Pharmacokinetic/Pharmacodynamic Studies

Competitive U19 Applications

- Multidisciplinary Team
  - Expertise for all components working together
  - Should also strive to include diversity in team members
  - Input from patients/caregivers encouraged
- Rational for Proposed Approach to Treating Pain
  - Should be supported by a cogent biological rationale for how the proposed approach will result in new and promising non-addictive treatment for pain
- Clinical Benefit of Potential Pain Treatment
- Therapeutic Development Plan
  - It is expected that you will be ready for to RFA-NS-21-010 at the completion of the U19 – 5 years
- Data Management
  - See website for more on HEAL data management. This is critical.
  - https://heal.nih.gov/about/public-access-data.
- Milestones

Milestones

- Annual **go/no-go** milestones must be proposed
- Quantifiable, well-described, and scientifically justified
- Gate beginning and ending of tasks AND individual components
  - Most research components will not span the full 5 years
- Specific Aims or a list of activities are not milestones!
- Because therapeutic discovery and development are high risk, there will be significant attrition of programs.

Example Milestones

- Developed assays will perform with the specificity and activity required for use as a compound or biologic screening method. Activity will be demonstrated by the following:
  - a. The **positive** control inhibits enzyme activity by >80%
    b. The **negative** control, does not inhibit enzyme activity (<5%)
    c. Receptor negative cells do not respond to the positive control (<5%)
- Developed assays will perform with the signal-to-noise, precision and dynamic range required for use as a compound or biologic screening method. Signal-to-noise, precision and dynamic range will be demonstrated by the following:
  - The Z' score will be ≥0.5, based on values from at least half a plate of positive and negative controls
  - The blinded test-retest reliability (r^2) will be ≤ 0.75 on at least 4 positive and 4 negative compounds
  - The positive control demonstrates a dose-response relationship.
- Developed assays will perform with the accuracy and precision required for use as a compound or biologic screening method. The reported accuracy and precision of the assay will be within 10% of a designated reference standard.

https://www.ninds.nih.gov/Funding/Apply-Funding/Application-Support-Library/IGNITE-Milestone-Examples

Milestones Review

- Proposed milestones: peer reviewed and are scored
- **Prior to award**, NIH program staff will contact you to finalize milestones based on review recommendation and RFA goals
- **Annual milestone evaluation** will be done via administrative review by NIH
  - Successful achievement of milestones
  - The overall feasibility of program advancement, considering data that may not have been captured in milestones
  - Competitive landscape for the disease indication and drug target
  - HEAL programmatic priorities
  - Availability of funds

5 Research Components

- Validation of Therapeutic Target and Underlying Biology
- Development and Validation of Animal Models and/or Outcome Measures
- Assay Development, Screening and Optimization
- Discovery and/or Validation of Pharmacodynamic Markers
- Efficacy and Pharmacokinetics/Pharmacodynamic (PK/PD) Studies

Validation of Therapeutic Target and Underlying Biology

- Describe the unique and innovative contributions that will be made by this project
  - Proposed therapeutic target(s)
  - Rigorous validation
  - Type(s) of pain or pain condition(s) or pain-associated with specific disease(s)
- Demonstrate little or no addiction potential
- Rigorously validate the target
  - Multiple animal models
    - reproducing the work in another laboratory
    - Consider experiments using human tissue
- Expand understanding of the underlying biology to support rational for therapeutics development

Development and Validation of Animal Models and/or Outcome Measures

- New models or ex vivo systems can be genetic, chemical, and/or physiological manipulations
- Should represent a significant advance over those that currently exist for defined pain conditions
- Should translate to human condition as best possible
- Should include internal and external validation. Include face, construct, and predictive validity (to the extent possible)

Assay Development, Screening and Optimization

- Should include plans for:
  - Development of in vitro and/or ex vivo assays
  - Screening and/or rational design efforts to identify and characterize novel assets for neurological disorder
  - Assets can be a small molecules or biologics
- Assays should be optimized, standardized and validated as needed for the screen
  - Throughput should be sufficient for needs of the project
- Applicants are encouraged to consult the NCATS Assay Guidance Manual

Discovery and/or Validation of Pharmacodynamic Markers

- PD markers represent target engagement (direct or indirect):
  - Represent endpoints that can be measured in both preclinical and clinical settings
  - Represent a significant advance over PD measurements that may already exist for the therapeutic agent and targeted pain condition
- Plans for internal and external validation

Efficacy and Pharmacokinetics/Pharmacodynamic (PK/PD) Studies

- Goal is to demonstrate that the proposed asset has sufficient biological activity to warrant further development to treat neurological disorders (entry criteria for RFA-NS-21-010)
- Pharmacokinetic measurements reflect the body's effect on the absorption, metabolism, distribution and excretion of the asset.
- Combined measurement of PK, PD and in vivo efficacy greatly increases understanding of an asset

Applications that are Nonresponsive

- Applications targeting opioid receptors
- Applications lacking milestones
- Applications lacking plans for at least 3 research components
- Projects in the lead optimization, IND-enabling or clinical stage (see RFA-NS-21-010)
- Technical development of neurostimulation or other medical devices for the treatment of pain
- Applications to develop disease initiation, remission, relapse, prognostic, diagnostic or prediction of progression biomarkers

Non-responsive applications will be withdrawn from consideration BEFORE review.

U19 Application Reviews

Goal of this FOA: Team-based research projects to develop assays, screening and early optimization work to develop non-addictive therapeutics to treat pain

Two Critical Review Goals

Application components:

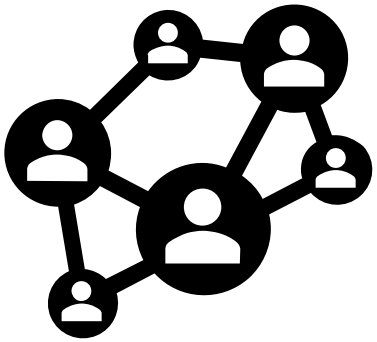
- a strong rationale
- rigorous supporting experimental data
- research team expertise
- rigorous research plan
- interdisciplinary team-based approach

to validate non-addictive pain therapeutic target(s) and therapeutic agent(s)

Evaluation on potential to meet entry criteria for next phase of translation (RFA-NS-21-010)

How the proposed integrated therapeutic development plan will likely generate a pain therapeutic asset to the point (within 5 years) where they can meet the entry criteria for: ***optimization & development of promising small molecule and biologic hits/leads to Phase-I CTs.***

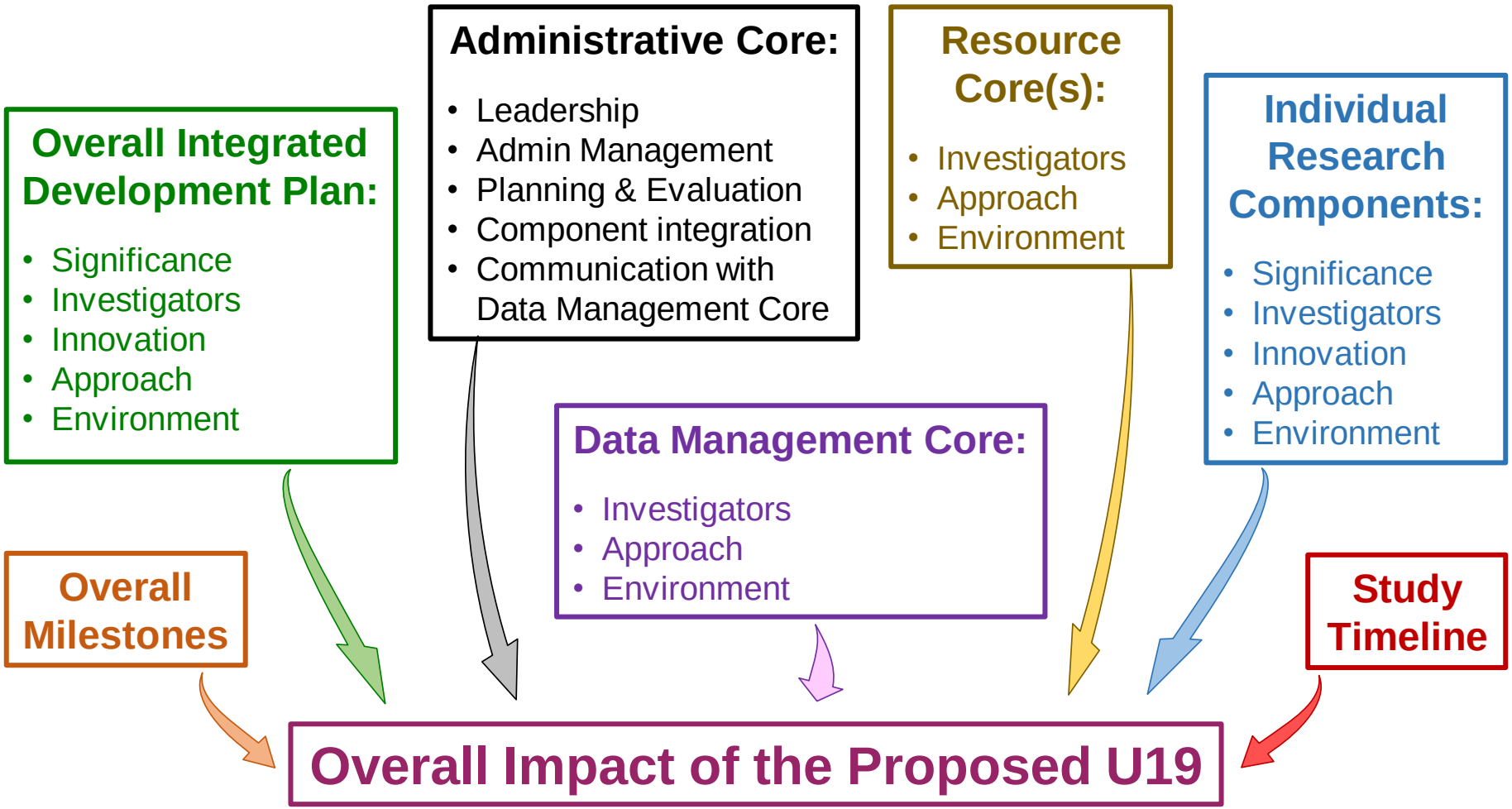
U19 Application Reviews



Application Evaluation Criteria

- ✓ Cohesiveness and synergy for the integrated research and therapeutic development plan proposed
- ✓ Relationship and contributions of the Research Components, Resource Core(s) and Data Management Core to the overall objectives
- ✓ Synergy between the components that could not be achieved through individual NIH award mechanisms
- ✓ Clear advantages of conducting the proposed therapeutic development plan as a collective team-based program rather than through separate efforts
- ✓ Relevant strengths and weaknesses of individual components in the context of the entire integrated pain therapeutic development plan
- ✓ Feasibility and meeting milestone requirements, since there is no opportunity for renewal of grant awards under this FOA

U19 Application Reviews: Review Criteria



U19 Application Reviews: Rigor & Reproducibility

- Is the rigor of the prior research that served as the key support addressed for each individual research component and for the overall integrated development plan?
- Are development and standardization of *in vitro*, *ex vivo* and *in vivo* assays for the proposed therapeutic agent scientifically sound and rigorous, in relation to the validated therapeutic target and related pain type(s)/indication(s) and/or disease-associated pain conditions?
- What is the likelihood that these assays will provide rigorous specificity testing and screening of the proposed therapeutic agent(s)?
- Does the experimental design include measures to reduce potential bias, including blinding, randomization, and inclusion/exclusion criteria?
- Is the data source used to calculate sample size estimates (power analysis) **and** details about the analysis itself included?
- Are the proposed plans for testing the efficacy and PK/PD characteristics robust? Will the PD and *in vivo* efficacy plan support future therapeutic development? Will it produce therapeutic agents that meet the entry criteria for the next optimization phase?

General Recommendations

- Carefully read the Funding Announcement
- Components should be integrated. Most components will not take the full 5 years. Have a clear plan for how one feeds into another and how this is milestone gated
- All 5 research components need to be included unless you can demonstrate that the work is already done
- Include clear, quantitative go/no-go milestones
- Discuss rigor, both in preliminary data and proposed experiments. (Rigor Guidelines)
- Discuss intellectual property plans; include letter from tech transfer office
- Discuss therapy development plan

More General Recommendations

- Include a multidisciplinary team
- The review panel will be multidisciplinary
- Contact NIH Program Staff in advance
- Demonstrate that you will meet the entry criteria for RFA-NS-21-010
- Pay attention to Human Subjects requirements
  - Not just clinical trials – human tissue is included

RFA-NS-21-010 - Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain (UG3/UH3)

The overall goal of this initiative is to support preclinical optimization and early Phase I testing to develop of safe, effective, and non-addictive small molecule and biologic therapies to treat pain.

- Accelerate the optimization and development of promising small molecule and biologic hits/leads into therapeutic agents
- Entry Criteria:
  - A rigorous biological rationale for the intended approach
  - A promising small molecule or biologic starting point for optimization
  - Scientifically sound assays to optimize and test the agent

Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain

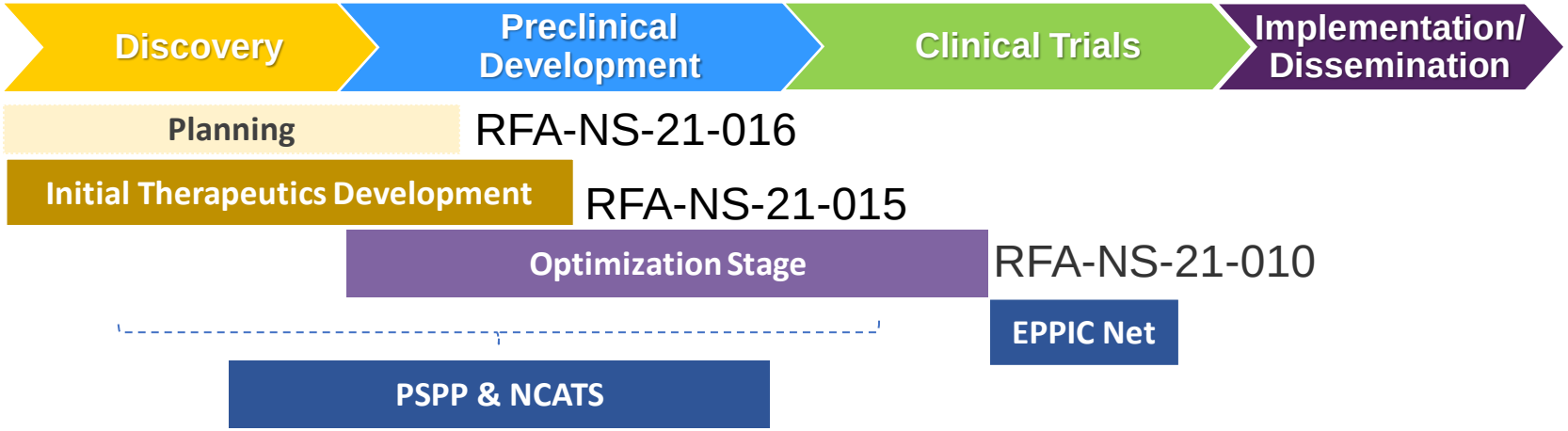
Goal

Accelerate development of novel, non-opioid, non-addictive analgesics

Five-year Benchmarks

- ✓ At least 5 promising projects with appropriate assay(s), model(s), and tools - ready for preclinical lead optimization.
- ✓ At least 3 novel analgesics with an IND and human safety data – ready for clinical efficacy studies through EPPIC-Net or equivalent phase II trial.

Proposed HEAL Analgesic Development Program



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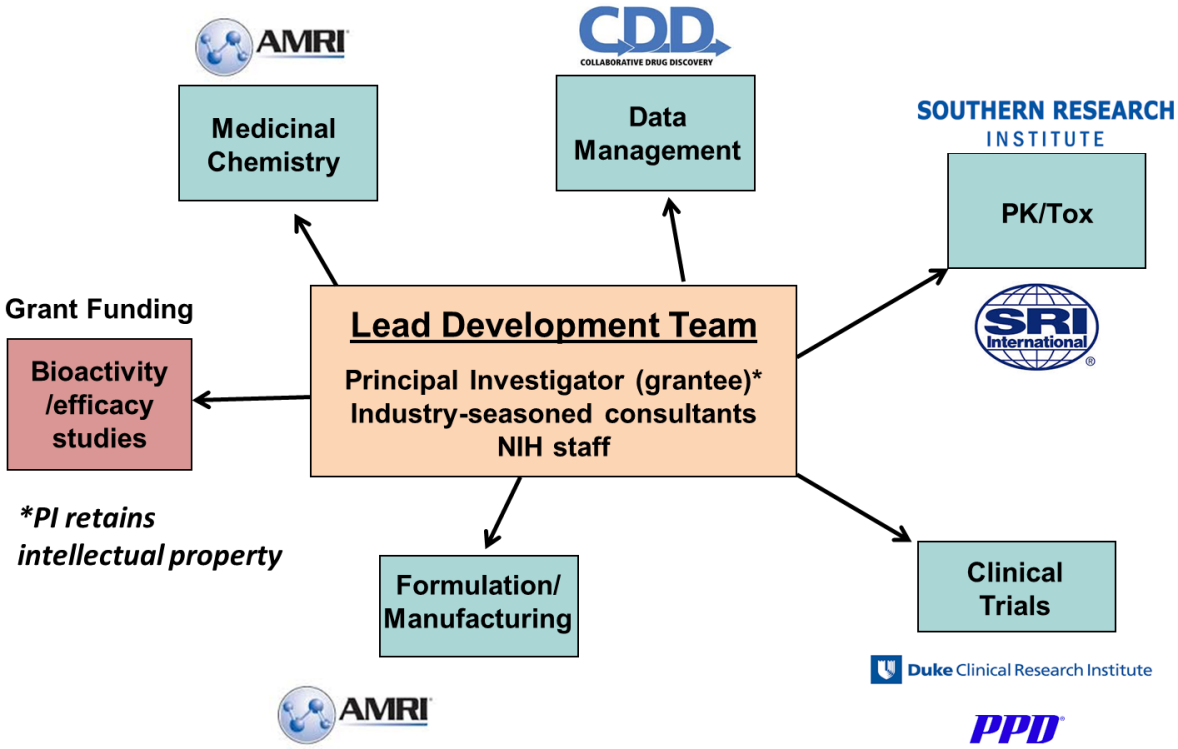
Provide Resources Not Readily Available in Academia



* Contract resources are tailor-made to support PI teams
(Other contracts may be implemented)

Webinar Questions?

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