Applicant Information Webinar for NIH Back Pain Consortium (BACPAC) Research Program
Webinar Logistics

- We will be recording and posting this webinar
- All participants will be muted
- A list of commonly asked FAQs are posted and will be updated on the BACPAC Website:
Comments

• Your line is muted

• Leave a comment in the chat box if you have problems hearing the presenter(s) or seeing content on the screen. We will respond via the chat function to help resolve the problem.
Questions

- You can ask questions via the “Q&A” box in the webinar (preferred).
- You can virtually raise your hand via the icon in the webinar.
NIAMS Team

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Grants Management Contact:
Erik Edgerton, M.B.A.
Agenda

• Introduction & WebEx overview – 5 min; Neil Roberts

• Program overview – 10 min; Susana Serrate-Sztein

• Review procedure & application deadlines – 5 min; Kan Ma

• Grants Management overview and Cooperative agreement overview – 10 min; Erik Edgerton

• Funding announcement overviews – 5 min each; Yan Wang; Charles Washabaugh; James Witter; Xincheng Zheng

• Q&A session – 40 min
HEAL Research Priorities

• Improve Treatments for Opioid Misuse and Addiction
• Enhance Pain Management

Back Pain Consortium (BACPAC) Research Priorities

Expand the number of therapeutic options to improve pain and function

Understand the mechanisms of low back pain

• Use novel technologies to identify new druggable disease mechanisms
• Develop precise diagnostic and treatment algorithms
• Tailor therapies to individual patients
• Test new therapies
Back Pain Consortium (BACPAC) Research Program

- FPRS Priority- targeted to low back pain

- Develop Approaches Incorporating the Principles of Precision Medicine to Prevent and Treat Chronic Pain

- The discovery and validation of markers, measures, and combinations of these factors predictive of an individual’s susceptibility to chronic pain of specific types is needed. Identification of patient-specific factors associated with favorable versus poor responsiveness to specific treatments. Establish genetic and environmental factors predictive of adverse treatment outcomes such as medication-related side effects, organ toxicity and addiction. Develop biostatistical methodologies to combine and weight patient specific factors for the purposes of enhancing diagnostic accuracy and optimizing treatment selection.
Background

Conclusions

- A number of pharmacological and nonpharmacological noninvasive treatments for low back pain are associated with small to moderate, primarily short-term effects on pain versus placebo, sham, wait list, or no treatment. Effects on function were generally smaller than effects on pain. More research is needed to understand optimal selection of treatments, effective combinations and sequencing of treatments, effectiveness of treatments for radicular low back pain, and effectiveness on outcomes other than pain and function.
Background

• In 2013, the NIH Pain Consortium established a Steering Committee for a Research Task Force (RTF) on Research Standards for cLBP.

• The RTF made recommendations for the use of a standardized consistent use of a definition of cLBP, a minimum dataset, and reporting outcomes.

• The RTF also made future research recommendations. They concluded that greater consistency in reporting should facilitate comparisons among studies and the development of disease phenotypes. https://www.ncbi.nlm.nih.gov/pubmed/24787228.

• Limited testing of new pharmacologic treatments on chronic low back pain (inflammation, peripheral pain transmission or amplification, central sensitization, and descending modulation)
Background

• Back pain is one of the most common forms of chronic pain among adults worldwide.
• Out of all 291 conditions included in the Global Burden of Disease 2010 Study, low back pain ranked highest in terms of years lived with disability.
• Back pain is over-represented among women and in people with low socioeconomic status. Children are also affected, a recent study indicated that the prevalence of low back pain in adolescents increases with age and reaches the levels observed in adults by age 18.
• There are disparities in the treatment of pain between whites and racial/ethnic minorities.
BACPAC Program Overview

Components

Systems Level Data Analysis
- Data, Algorithm and Research Program Management Center
- Technology Sites
- Mechanistic Research Centers

Clinical Data Standardization/Integration/Analysis
- Collaborative Adaptive Multimodal Clinical Study

EPPIC

Phase 2 Trials
Collaborative Work

- **Focus on Discovery**
- **Consensus development process to select**
  - cLBP definition
  - Common minimal dataset
  - Outcomes
  - Patient Phenotyping
    - Clinical Management Committee/DAC

- **Conduct Adaptive Design Clinical Study(ies)**
  - Design, conduct, analyze results
BACPAC Program Overview

Clinical Cohorts
• be existing and ongoing with a minimum of 100 consented patients
• Include current and proposed methods for deep clinical phenotyping
• Include PROs and patient reported preferences and values related to treatments, healthcare states, and outcomes
• Be available for studies in other centers

Collaborative Clinical Adaptive Study
• subjects prospectively assigned to one or more interventions to evaluate the effects on health-related biomedical or behavioral outcomes
• use multimodal therapy approaches
• emphasize innovation in trial design (SMART, adaptive design, T2T, etc.)
• carried out collaboratively
Sharing and Integration

- Information
- Technology, methodology and approaches
- Data (clinical and other data generated by the MRCs and Tech Sites): Systems Biology and Clinical Integration
- Patient cohorts and specimens
- Algorithm development
- Timelines: project, center/site/consortium
Interactions

• Within the Consortium
• With the Early Phase Pain Investigation Clinical Network (EPPIC-Net).
• With other HEAL projects
BACPAC Program Overview: Expected Outcomes

• Integrated model of LBP through improved understanding of mechanisms, leading to new therapies

• Algorithms to match patients to best treatments based on extensive phenotyping

• Safety and Efficacy Data on new therapies that can move to Phase 3 Trials

• Clinical studies combining multimodal interventions with deep phenotyping and patient-reported symptoms and outcomes
Overview of Scientific Review Process

Kan Ma, NIAMS
Review Process

• All four FOAs will be reviewed by NIAMS Scientific Review Branch.

• Review meetings will be face to face between May and July 2019 for August 2019 council.
  - Review in May/June, 2019
    - RFA-AR-19-029 (UG3/UH3)
  - Review in June/July, 2019
    - RFA-AR-19-026 (U19)
    - RFA-AR-19-027 (U24)
    - RFA-AR-19-028 (UH2/UH3)

• Reviewers will be recruited for each project or each component type based on the expertise needed and area of research.
Review Criteria

• Reviewers use different sets of review criteria for each FOA based on the specific review criteria listed in the FOA.

• In addition to the standard review criteria, please pay attention to the criteria *Specific to each FOA*.

• Each application will receive a numerical impact score and five criterion scores.

RFA-AR-19-026 (U19)

• The Overall Center, Administrative Core, Research Project(s) and other Core(s) will each receive a numerical impact score. In addition, the Overall Center application and the Research Project(s) will receive an individual criterion score for each of the 5 review criteria.

• The overall impact score for a U19 Center will reflect an integrated assessment of the whole application, including not only the quality of the individual components but also how the proposed Center will bring together all these elements in a cohesive unit.
Key Dates and Timeline

- **Letter of Intent Due:**
  - RFA-AR-19-026 (U19): February 18, 2019

- **Application Due:** March 20, 2019
  *No late applications will be accepted.*

- **Peer Review:** between May and July, 2019

- **Council Review:** August 2019

- **Anticipated Earliest Start:** September 2019
Overview of Grants Management Process

Erik Edgerton, NIAMS
Cooperative Agreements: U Mechanism

- Used when substantial programmatic involvement is anticipated between the Federal agency and the recipient during performance of the assisted activity.
- Supports and stimulates the recipients' activities by involvement in and working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities.
- The Cooperative Agreement Terms and Conditions of Award in each FOA clearly outlines the roles and expectations of the PD/PI and NIH Staff.
- This information will also be included as a term of award on the Notice of Award (NoA).
Cooperative Agreements Terms and Conditions of Awards

• Acceptance of the Notice of Award (NoA) indicates the recipients’ willingness to work with NIH Program staff during the course of the award.
  – To participate in semi-annual meetings and in regular conference calls with NIH program staff and other BACPAC grantees.
  – To actively seek input from NIH regarding resource needs or expertise needs that may arise during the performance of the project.
  – To work within a consortium agreement to meet the goals of the Program.
  – Individual award budgets are subject to change as directed by the Steering Committee and based on the needs of the BACPAC Research Program Agenda.
Transition Phases

- The transition from one phase to the next (UH2/UG3 to UH3 phase) is gauged on the achievement of the negotiated milestones during an administrative review. Some of the following are general points that are considered:
  - Ability to work within a Consortium arrangement with other awardees to meet the goals of the program
  - The availability of funds
  - Program priorities
  - Successful achievement of the defined milestones for the UG3/UH2 Phase of the project
  - Milestones will be included in the Notice of Award
Cost Matching

• For-Profit Organizations only
  – Must match funds at a rate of not less than 50% of the total-Federally awarded amount, (1/3 of total cost) as stipulated by Public Law 115-141.
  – Must demonstrate that matching funds and/or in-kind contributions are committed or available at the time of award.
  – Applications must identify the source and amount of funds proposed to meet the matching requirement and how the value for in-kind contributions was determined.
HEAL Initiative: Back Pain Consortium (BACPAC) Research Program Data Integration, Algorithm Development and Operations Management Center (DAC) (U24 Clinical Trial Not Allowed) RFA-AR-19-027

Yan Wang, NIAMS
Research Objectives

• Guides and coordinates all activities of the BACPAC and ensure communications, interactions, synergies and accountability
• Establishes a central database system for the BACPAC that includes clinical and research data and ensure data accessibility, archiving and transfer
• Provides fiscal oversight and funds management
• Interfaces with EPPIC-Net in support of BACPAC Phase 2 trials
• Supports all aspects of clinical research carried out by the BACPAC, e.g. clinical registry, development of common protocol elements and collaborative clinical project protocol(s), etc.
• Conducts systems level analysis of multidimensional datasets generated by the Consortium to produce an integrated model of LBP
• Develops patient-centered algorithms for prediction of optimized therapeutic interventions using data from clinical studies across the Consortium
Research Scope

• Areas of Responsibilities
  ➢ Clinical Registry, Data Integration and Coordination
  ➢ Adaptive Design, Patient Reported Outcomes (PRO) and Biostatistics
  ➢ Algorithm Development, Testing and Validation
  ➢ Systems Biology and Bioinformatics
  ➢ Operations Management

• Dynamic interactions and collaborations among the teams and with the experts on the various BACPAC committees and functional working groups
Application Instructions (Section IV of the FOA)

Important instructions to keep in mind:

• In lieu of a standard Approach section as described in the SF424 (R&R) Application Guide, the applicant must present a discussion of the planned activities to carry out functions in the 5 areas listed on the previous slide.
• Must include appropriate expertise and qualified key personnel in all functional areas.
• Must demonstrate experience with clinical trials or studies.
• Must include a description of Database Building Capacity.
• Other Attachments:
  ➢ Applications must include an Intellectual Property (IP) strategy.
  ➢ Applicants may propose one or more concept(s) for future Pilot Research Projects and Ancillary Studies.
Page Limits for Components

All page limitations described in the SF424 Application Guide and the Table of Page Limits must be followed.

<table>
<thead>
<tr>
<th>Section of Application</th>
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HEAL Initiative: Back Pain Consortium (BACPAC) Research Program: Mechanistic Research Centers (U19 Clinical Trial Optional)

RFA-AR-19-026

Charles Washabaugh, Ph.D., NIAMS
Research Objective

Goals:

• To improve the understanding of disease, generate new information that contributes to accurate patient phenotyping and identify novel pathways and targets for intervention.

• The MRCs will also use adaptive novel study designs and multimodal therapies to understand the basis for patient treatment responses and improve the targeting of effective treatment to individual patients.

• The investigator has the flexibility to design a BACPAC Mechanistic Center with optimal structure to foster synergistic interactions or maximize integration and productive interdisciplinary collaborations.
Research Scope

Address either a **scientific theme** or a **scientific challenge** in low back pain (LBP)

Designed to

- Improve understanding of the mechanism of action of the intervention or pathogenesis of the disease
- Address fundamental questions about back pain

Use analytics (assays, instruments, tests, methods, etc.) to generate data that

- Improve understanding of LBP
- Improve phenotyping of LBP patients
- Can be used in the generation, modification and refinement of algorithms that help match patient phenotypes with best available or new therapies

Must be linked to either a clinical prospective BP observational cohort and/or a clinical trial

Data are shared with other centers, and systems level data analysis is conducted to produce an integrated model of LBP
Components of the BACPAC U19 Center

Four **required** components of a Mechanistic Research Center (MRC):

1. A strong research program focused on back pain consisting of **one or more translational Research Projects** and **one or more Research Cores** focused on the translation of new scientific findings and technological development into better approaches for improving the lives of patients with chronic back pain.

2. A **Clinical Core** that includes an existing, ongoing well characterized back pain cohort with the capacity to rapidly expand enrollment.

3. An **Administrative Core** with an Advisory Committee that includes scientific and lay members.

4. An **Informatics Core** that will conduct data collection/management activities to support the clinical and research activities of the MRC.

*To be considered complete, a Center application will need a minimum of three Research Cores or Projects, in any combination, in addition to the required Administrative, Clinical and Informatics Cores.*
Additional Considerations for the U19

- May propose one or more concepts for a future Pilot Research Project(s) and/or Ancillary Studies with a budget in the admin core beginning in Year 2
- Applications must include an Intellectual Property (IP) strategy.
- Applications are due March 20th 2019
- Letter of Intent should be submitted 30 days (Feb 18th) prior to application due date.
- The NIAMS intends to commit up to $15.1M in FY 2019 to fund 3-5 awards.
- Application budgets are not limited but need to reflect the actual needs of the proposed project.
- The maximum project period is 5 years.
# Page Limits for Components

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<th>Available Component Types</th>
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HEAL Initiative: Back Pain Consortium (BACPAC) Research Program: Phase 2 Clinical Trials (UG3/UH3 Clinical Trial Required)

RFA-AR-19-029

James Witter, NIAMS
Research Objective

• Despite a pipeline of interventions that target inflammation, peripheral pain transmission or amplification, central sensitization and descending modulation, there are no consistently effective and durable treatments for chronic lower back pain (cLBP)

• Therefore, the purpose of this FOA is to facilitate the planning (UG3) and execution (UH3) of patient-centric, stratified, clinically-meaningful phase 2 clinical trials that are part of the larger BACPAC Initiative.

• The goal of the Phase 2 CT will be to generate data on safety and efficacy of new interventions using the most scientifically rigorous approaches.

• Types of applicable clinical trials can include the traditional randomized controlled designs, however, the use of novel, efficient complex adaptive designs that may employ Bayesian approaches or master protocols that include umbrella or platform designs are encouraged in this FOA.

• Designs may be modified from their original UG3 planned format based on new information or mechanistic targets established early in the Initiative.
Research Scope

• Phase 2CT in cLBP intended to test repurposed or novel, non-addictive drugs, biologics, devices, or CAM conceptualized/implemented with a biopsychosocial perspective to address physical, mental and social aspects

• Although these trials will interact/synergize with other components of BACPAC and NIH, they will use the EPPIC-Net Hubs, CCC and DCC and will be under EPPIC-Net Governance/Standards

• Investigators are encouraged to consider using the PROMIS® domains related to pain such as pain interference, physical function and depression

• Investigators will lead a single UG3/UH3 Phase 2 CT that is based on a strong scientific premise
Application Instructions Specific to RFA-AR-19-029

The complete application instructions can be found in section IV of the FOA

Important instructions to keep in mind:

• Letter of Intent
  – By the date listed in Part 1. Overview Information, prospective applicants are asked to submit a letter of intent (Jan. 26, 2019)

• Applications (due Feb 26, 2019) must include attachments that discuss Clinical Trial Experience, the Schedule of Events, and the Milestone Plan. If they are missing the application will be considered incomplete and will be withdrawn.

• In addition, applicants may propose one or more concepts for future Pilot Research Projects and Ancillary Studies. Label the file "Pilot.pdf"
Page Limits for Components

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Timeline

Planning Phase (up to 2 years)
• clinical trial planning
• development of protocols and associated study documents with the BACPAC CMC and the EPPIC-Net CCC and DCC

Implementation Phase (up to 4 years, entire grant no more than 5 years)
• conduct the clinical trial
• utilize the infrastructure of the EPPIC-Net to provide scientific guidance and coordination

UG3/UH3 Transition
• Programmatic review by NIH
• Successful achievement of negotiated milestones
• Availability of funds
Milestones and Budget

- **Milestones:**
  Applications must include well-defined milestones for the planning phase (UG3) and annual milestones for the implementation phase (UH3). Prior to a pending award, the PD/PI and NIH will negotiate a final list of milestones for each year of support. UG3 funding does not guarantee subsequent UH3 funding.

- **Award Budget:**
  The application budgets for UG3 planning phase (up to 8 awards will be made) are limited to $200,000 Direct Costs for the entire planning phase. The application budgets for UH3 phase (up to 5 awards will be supported) are not limited but need to reflect the actual needs of the proposed project.
HEAL Initiative: Back Pain Consortium (BACPAC) Research Program Technology Research Sites (UH2/UH3 Clinical Trial Optional)

RFA-AR-19-028

Xincheng (Ted) Zheng, NIAMS
Research Objectives:

• Technology Research Sites will support projects to develop, validate, optimize and translate promising tools, technologies and/or methods (TTM) that will lead to a better understanding of mechanisms of low back pain, sub-phenotyping of patients with chronic low back pain (cLBP), and identifying new targets for intervention. Ultimately this will improve the diagnosis, treatment of cLBP and prevention of the transition from acute to chronic LBP.

• TTM that are successfully developed might be deployed in the clinical trials supported by BACPAC, including Phase 2 CTs and/or the Consortium-wide multimodal adaptive trial.
Areas of Interest include but not limited to:

• **TTM to enable phenotyping and sub-phenotyping**, and evaluation and prediction of likelihood of treatment response.
• **Sensor-driven, implantable devices** to target peripheral pain pathways, or to monitor/track cellular and molecular changes, alterations in either structure or function of tissues and organs involved in cLBP.
• **Wearable technologies** to target peripheral and central pathways involved in cLBP and to counter decreases in physical function and disability to inform or provide clinical treatment.
• **Wearable technologies** to record patient reported outcomes.
• **Modeling and three-dimensional human tissue system** that mimics in vivo tissue architecture and physiological conditions to facilitate and accurately monitor key organ-level functions of chronic low back pain.
• **Clinical non-invasive or minimally invasive assessment and/or imaging tools** to precisely locate pain-related neural circuits. This personalization will inform development and use of next-generation neurotherapeutic devices by identifying targets for intervention.

This RFA will NOT support:

• cLBP due to metastatic bone disease, acute or chronic infection or acute trauma;
• Biomarker discovery or validation;
• Development of new drugs;
• Animal model: Research involving the use of animal models is not excluded; however, any proposed animal model(s) must be highly relevant to human conditions and the demonstrated application to humans must be included in the specific aims of the proposed project(s).
Different Developmental Phases of TTM:

I. **Exploratory Research for Technology Development:** This is high risk, preliminary research that, if successful, should lead to a preliminary demonstration of feasibility. Experimental results from the exploratory project should serve as a foundation for next stage of development. It is expected that projects in this category generally will not have preliminary data.

II. **Focused Technology Research and Development:** Projects are characterized by project addressing unmet technical challenges that are associated with the early stage development that lead to create an effective TTM for cLBP research. Well characterized physiological, psychological systems and standard experimental approaches in pain research are appropriate as model systems to evaluate and demonstrate performance of the TTM. Project aims should be closely associated with technical milestones that represent meaningful benchmarks for the performance of the technology. Projects in this category generally have preliminary data demonstrating feasibility of the approach but may still have some elements of risk.

III. **Iterative Technology Research and Development:** Projects are characterized primarily by the close coupling of the technology development with the application of emerging technologies to biomedical projects that serve as test-beds. Technologies are at a stage in which they can be tested in research for continued development and improvement.

IV. **Research and Development for Technology Optimization:** Projects are characterized by refinement of existing technologies with high clinical impact on cLBP and making them transferrable to other research and clinical sites participating in the BACPAC. Projects in this category can demonstrate the utility of an available TTM from other research field for a novel use in cLBP research, or repurpose a drug, biologic or device developed or approved for a completely different indication for the treatment of cLBP.
**Timeline**

**Exploratory Phase** (up to 2 years)
- Develop new or adapt/improve existing TTM
- Demonstrate proof-of-concept, feasibility and suitability for the next stage development

**Year 1**

**Year 2**

**Year 3**

**Year 4**

**Year 5**

**Implementation Phase** (up to 4 years, entire grant no more than 5 years)
- Optimization and validation of the TTM developed in its UH2 phase
- Demonstration of performance, effectiveness, and promise of the TTM for mechanistic and/or clinical utility
- Clinical trials, if applicable
Milestones and UH2/UH3 Transition:

Transition Milestones to the UH3 phase and Timeline:
- A required specific section.
- Must be well defined, quantifiable milestones to the UH3 phase.
- Examples of well-defined milestones are:
  - results that support, reject, or are inconclusive regarding testing of their concept/hypothesis;
  - appropriate objective performance targets;
  - quantitative indicators for go/no go decision points such as an appropriate level of detection and coefficient of variation, or sensitivity and specificity;
  - timelines for assessing progress, including specific milestones for progressing from the UH2 to the UH3 funding periods.
- Additional Review Criterion that affects the overall impact score.

Criteria for evaluation of the UH2 transition to UH3:
- Successful completion of the UH2 milestones;
- Feasibility to apply the Tech Site’s TTM to ongoing and planned research projects and trials in the BACPAC Consortium;
- Available patient populations and statistical design considerations;
- Potential for meeting the goals of BACPAC Research Program, including contributions to collaborative activities;
- Availability of funds
RFA Specifics:

• Eligibility: Domestic and international institutions are eligible.
• Clinical trial optional.
• Other attachment and additional review consideration:
  Intellectual Property Strategy (3 pages): Describe the IP landscape surrounding TTM; IP status or filing plan; any known constraints that could impede sharing of the TTM.
• Page limitations: 12 pages. This total page limit can be divided into UH2 and UH3 phase as applicants deem appropriate.
• Award Budget: $2.6M to fund 4-6 awards, UH2 award does not guarantee subsequent UH3 funding;
  UH2: Up to $400,000/year for up to two years;
  UH3: not limited but need to reflect the actual needs of the proposed project.
• Multi-PI applications: allowed.
Questions?

• You can ask questions via the “chat” function in the webinar (preferred).

• You can virtually raise your hand via the icon in the webinar.
Thank you!