Social Drivers of Mental Illness in Low and Middle-Income Countries: Mechanisms and Pathways of Interventions for Youth

Technical Assistance Webinar
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Overview of RFA-MH-21-160: Goals

RFA-MH-21-160 Social Drivers of Mental Illnesses in Low- & Middle-Income Countries: Mechanisms and Pathways of Interventions for Youth

Goal: Solicit research that identifies and explains the mechanisms and pathways by which social drivers affect youth mental health.

- Participants: age 5-24 years, living in LMIC.
- LMIC: Low, lower middle, and upper middle-income countries according to current World Bank designation or prior designation before January 1, 2021.
- Innovative approaches to capture real-world complexity.
- Applicants from US and upper-income countries encouraged to partner with LMIC sites. Projects which build research capacity are welcome.
- Applications may propose new studies or secondary data analyses.

Emphasis on specifying models, variables, and measures to identify and test potential pathways and mechanisms that account for changes in key outcomes. Must be consistent with the NIMH Experimental Therapeutics Approach. Use of the RDoC Research Framework is encouraged.
The NIMH Experimental Therapeutics Approach

Studies that include the development and testing of therapeutic, preventive, and services interventions are required to not only evaluate the clinical effect of the intervention, but also generate information about the mechanisms underlying a disorder or an intervention response.

- Identification of the targets or mediators of an intervention
- Demonstration that the intervention engages and acts on the target, and results in improvement of clinical symptoms.

Why? Clinical research studies that measure only clinical outcomes do not tell us why the intervention works. If there is no improvement in clinical symptoms, we have not gained knowledge that will inform future trials.

What is a target? It can be a neural pathway, key cognitive operation, interpersonal or contextual factor that is hypothesized to mediate the intervention’s effect. While many NIMH studies measure cellular or neural processes, targets do not have to be biological or physiological.
NIMH Experimental Therapeutics Approach: Example

An investigator proposes that social isolation and decreased affiliation contribute to high rates of adolescent suicide and plans to investigate the effects of participating in a community social service program that involves peer interactions and positive relationships with adult group-leaders.

Putative targets = social isolation/belongingness, affiliation.

**Measures:** NIH Toolbox measures for friendship, emotional support, and loneliness at the start of the service program, and then monthly for 6 months. The Columbia Suicide Scales are used to assess suicidality. PHQ-9 utilized to assess mental health symptoms, including depression. Daily diaries including structured questions with rating scales as well as free-report will be used to measure daily social interactions and social context.

**Planned analyses:** The study will examine how the dependent measures change with duration of involvement in the program, size of group, type of service, characteristics of adult mentors, composition of group (same or mixed gender) and examine age, sex, gender, history of adverse childhood experiences.

**Hypotheses:** Participation in the program will lead to increased friendship and belongingness, increased emotional support, decreased loneliness, anxiety, and depression. The amount of change over time will be larger for individuals with multiple ACEs.
Research Domain Criteria (RDoC) framework

**Q: What is RDoC?**

**A:** RDoC is a research framework for investigating mental disorders. It integrates many levels of information (from genomics to behavior and self-report) to explore basic dimensions of functioning that span the full range of human behavior from normal to abnormal.

The RDoC framework is a research strategy that is implemented as a matrix of elements. The matrix is a dynamic structure that currently focuses on six major domains of human functioning (e.g., Negative Valence Systems, Cognitive Systems). Contained within each domain are several behavioral elements, or dimensional *constructs*, that comprise different aspects of its overall range of functions and are affected by environmental and neurodevelopmental contexts.
Research Domain Criteria (RDoC) framework: Example of Domain and Constructs

Domain: Negative Valence Systems

• Construct: Acute Threat ("Fear")
• Construct: Potential Threat ("Anxiety")
• Construct: Sustained Threat
• Construct: Loss
• Construct: Frustrative Nonreward

Acute Threat:

• Molecules: oxytocin, serotonin
• Circuits: amygdala, OFC
• Physiology: BP, eye tracking, respiration, heart rate
• Behavior: facial expression, response time, approach
• Self-Report: fear survey schedule, SUDS
• Paradigms: fear conditioning, Trier Social Stress test
Research Domain Criteria (RDoC) framework: Q&A

Q: How can I learn more about RDoC?
A: NIMH provides a website with details about the RDoC matrix and other resources: https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/index.shtml

Q: Do I have to include biological, neural, or genomic measures in my research in order to be aligned with RDoC?
A: NIMH does not expect every research study to be able to include cellular, neural, or genomic measures, especially in low resource or community settings. The RDoC research framework emphasizes mechanisms and constructs instead of clinical symptoms. Levels of analysis also include physiological (e.g. cardiac rhythm, blood pressure, actigraphy), behavior, and self-report measures.

Q: Am I limited to constructs in the RDoC matrix?
A: No. The matrix was intended to evolve over time and to represent consensus of the research community. Fundamental to using the framework is investigation of key constructs for one of the 6 domains and utilizing measurements at multiple levels of analysis. Flexibility in choice of constructs and measures is allowed.
Overview of RFA-MH-21-160: Review Criteria

Section V of the RFA lists the review criteria for this funding opportunity. Investigators are encouraged to familiarize themselves with the questions and evaluate how well their application will meet these criteria.

In addition to standard criteria, evaluation will include:

• To what extent the application includes significant involvement of researchers in LMIC?
• How well the application provides evidence that outcome measures are valid and reliable for the proposed population?
• How appropriate are models and measures that are used to test potential pathways and mechanisms?
• To what extent does the application employ objective and validated measures?
• Are the design and methods appropriate for the NIMH experimental therapeutics approach?
• If RDoC-like constructs have been proposed, does the application appropriately define biomarkers, mechanisms, intervention targets, and outcomes?
Overview of RFA-MH-21-160: Timeline

Letter of Intent Due Date: February 18, 2021 (optional, but encouraged)
Application Due Date: March 18, 2021
Scientific Merit Review: July 2021
Advisory Council Review: October 2021
Earliest Start Date: December 2021

**Question: What are the benefits of submitting a letter of intent (LOI)?**

**Answer:** LOIs allow NIMH review officers to anticipate the types of expertise that will be needed for the review panel, and to also plan for potential institutional conflicts of interest. Optimization and customization of the review panel benefits all applicants.
Additional Information

Thank you for expressing interest in the Social Drivers of Mental Illnesses RFA!

This presentation will be posted on the Center for Global Mental Health website: https://www.nimh.nih.gov/about/organization/cgmhr/index.shtml

Submit general questions to the Q&A box. We’ll be answering these now...

For specific questions about potential research projects, please feel free to contact:
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