Informational Pre-Submission Webinar
RFA-HD-25-002: Centers for Collaborative Research in Fragile X and *FMR1*-Associated Conditions

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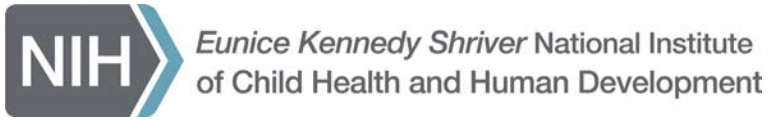


Webinar Basics

- All participants are being muted on entry
- Please type your questions into the “Q&A” box – we will have a live Q&A session at the end of the prepared presentation
- If you have questions that do not get answered during this session, please submit them by email to parisima@mail.nih.gov.
- We will post these slides, the webinar recording, and FAQs on the website for the Centers for Collaborative Research in Fragile X and *FMR1*-Associated Conditions: https://www.nichd.nih.gov/research/supported/ccrfx

Outline

- Refresher: NIH Strategic Plan for Research on *FMR1*-Associated Conditions
- Discussion of Current Funding Opportunity: **Centers for Collaborative Research in Fragile X and *FMR1*-Associated Conditions** (RFA-HD-25-002)
- Live Q&A

NIH Strategic Plan for Research on *FMR1*-Associated Conditions

- Four Areas of Interest:
  - Fragile X Syndrome (FXS)
  - Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)
  - Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)
  - *FMR1* Premutations
- Cross-Cutting Themes:
  - Infrastructure, Research Training, and Career Development
  - Promoting Collaborations Between Basic Scientists and Clinicians
  - Ethical, Legal, and Social Issues in Premutation Screening and Testing

Access the full Strategic Plan (PDF 1.84 MB).

Current Funding Opportunity

Centers for Collaborative Research in Fragile X and *FMR1*-Associated Conditions (P50, Clinical Trial Optional)

RFA-HD-25-002

The Basics

- Submission Deadline: August 20, 2024
  - Letters of Intent requested by July 6, 2024
- Budget Limit: $1.2M/year direct costs
- Anticipated number of awards: 3
  - Contingent upon availability of funds and submission of a sufficient number of meritorious applications
- Mechanism: P50 (Specialized Centers)
  - 1 administrative core
    - No other cores
  - 2-3 research projects
- Sponsoring Institutes & Centers
  - NICHD, NIMH, NINDS, NIDCD

Key Principles

- Specific Areas of Research Interest
- Major Changes from Previous RFA
- Highlighted Requirements
- “Clinical Trials Optional” – What does that mean in this RFA?
- Data and Resource Sharing

Purpose

- Address complex, difficult-to-solve problems in FMR1 research that are not readily addressed by standard investigator-initiated mechanisms
- Projects must be interdependent and interrelated, focused on a common unifying theme
  - Projects may share materials, results, data, patient populations, or methodologies
  - Results from one project may affect understanding and interpretation of data from other project(s) within the center
- Applications should propose research that can be completed within a 5-year grant period

Specific Areas of Research Interest

- Projects must address one or more of the following three priority research areas drawn from the FMR1 Strategic Plan:
  - Characterize phenotypes of FMR1-associated conditions and risk factors for disease severity across developmental stages and diverse populations
  - Identify novel mechanisms and targets for intervention across models of FMR1-associated conditions
  - Develop and validate translatable biomarkers and/or outcome measures for potential use in clinical trials
- Applications that do not address one or more of these priority research areas will not be considered responsive to this funding opportunity.

Specific Areas of Research Interest (cont.)

- **NICHD:** clinical and translational research to elucidate biological mechanisms, novel therapeutic targets and outcome measures, and/or drivers of phenotypic heterogeneity in FXS and FXPOI in NICHD populations of interest, including infants, children, pregnant people, and women
- **NIMH:** FXS research that examines co-occurring mental health conditions
- **NINDS:** research aimed at understanding motor and cortical functions in FXS and FXTAS as they relate to neurodevelopment and neurodegeneration. Studies focused on the cellular and molecular mechanisms that drive circuit dysfunction are of particular interest.
- **NIDCD:** research that examines hearing, balance, taste, smell, voice, speech, or language in individuals with FXS and *FMR1*-Associated conditions

Major Changes from Previous RFA

- All centers must include at least one project that involves human subjects or human phenotypic data. Projects that exclusively use human cells or human-derived materials, while welcome in center proposals, do not satisfy this requirement.
- Each project must clearly describe the range of genetic/strain backgrounds that will be utilized and justify why the distribution is sufficient to address the project objective(s) and the overall theme of the center.
- No individual may serve as key personnel on more than one application submitted to this funding opportunity.

Major Changes from Previous RFA (cont.)

- Projects involving animal models must use multiple background strains and/or species to model the impact of varying genetic backgrounds/epigenetic variation on specific phenotypes or disease mechanisms.
- Applicants must submit a Plan for Enhancing Diverse Perspectives (PEDP).
- Applicants must discuss how their Center will engage respectfully with stakeholders (including patients, families, their representatives, and health professionals) to promote equitable and bidirectional knowledge transfer between investigators and community members, including those from populations that experience health disparities.

Major Changes from Previous RFA (cont. 2)

- All applications should describe how standardization of data collection and data collection instruments – including the use of existing NIH common data elements (CDEs) – will be promoted and how these data collection techniques will facilitate data integration and collaboration.
- NIH strongly encourages Centers to design at least one Research Project that includes as key personnel an investigator who meets the NIH definition of an Early-Stage Investigator (ESI) at the time of application submission.

Requirement: Overarching Theme

Each center will be required to identify an overarching theme directed at one or more of the following three research areas in one or more FMR1-associated condition(s):

- Identifying, characterizing, and/or modeling factors that predict subgroup- or individual-level differences in clinical features ("phenotypic heterogeneity") and/or responses to specific interventions
- Identifying novel mechanisms and targets for intervention that modulate symptom severity or therapeutic efficacy
- Identifying and/or validating translatable biomarkers and/or outcome measures for potential use in clinical trials

Requirement: Multiple Levels of Analysis

Centers must propose hypothesis-driven projects that include at least two distinct levels of analysis within one or more strains or species.
(The multiple levels of analysis can occur across two or more projects.)

Requirement: Multiple Levels of Analysis (cont.)

- Studies involving brain/behavioral outcomes should choose at least two from among the following levels of analysis:
  - genomic/molecular measures
  - circuit/network measures
  - clinical/behavioral measures
- Studies involving outcomes in other organ systems or clinical domains should choose at least two from among the following levels of analysis:
  - genomic/molecular measures
  - tissue-specific/organ-level measures
  - clinical/whole organism measures
  - endocrine measures (for studies involving reproductive outcomes)

Requirement: Plan for Enhancing Diverse Perspectives (PEDP)

- All applications must include a PEDP, which will be assessed as part of the scientific and technical peer review evaluation.
  - The PEDP must be submitted as an “Other Attachment” included with the Overall Component. (Note: the PEDP does not count against the Overall Component page limit.)
- Applications that fail to include a PEDP will be considered incomplete and will be withdrawn before review.
- PEDPs may be no more than **two** pages in length and should include:
  - Actionable strategies using defined approaches for the inclusion of diverse perspectives in the project;
  - Description of how the PEDP will advance the scientific and technical merit of the proposed project;
  - Anticipated timeline of proposed PEDP activities;
  - Evaluation methods for assessing the progress and success of PEDP activities.

Requirement: Justification of Center Mechanism

Each application must:

- Describe the relationship of each project to the overall theme of the Center and the interactions with other Research Projects, and
- Present a compelling case describing how collaborations between projects and participating investigators are expected to yield results beyond those achievable if each project were pursued separately and without formal interaction among the participating investigators.

Requirement: Justification of Range of Backgrounds

Each application must:

- Describe the range of backgrounds that will be utilized for any subjects, animal models, or source materials/data, and
- Justify why the distribution of backgrounds within and across projects is sufficient to address the Center's overarching theme and specific aims.

How Does NIH Define a Clinical Trial?

*A research study in which one or more **human subjects** are **prospectively assigned** to one or more **interventions** (which may include placebo or other control) to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes**.*

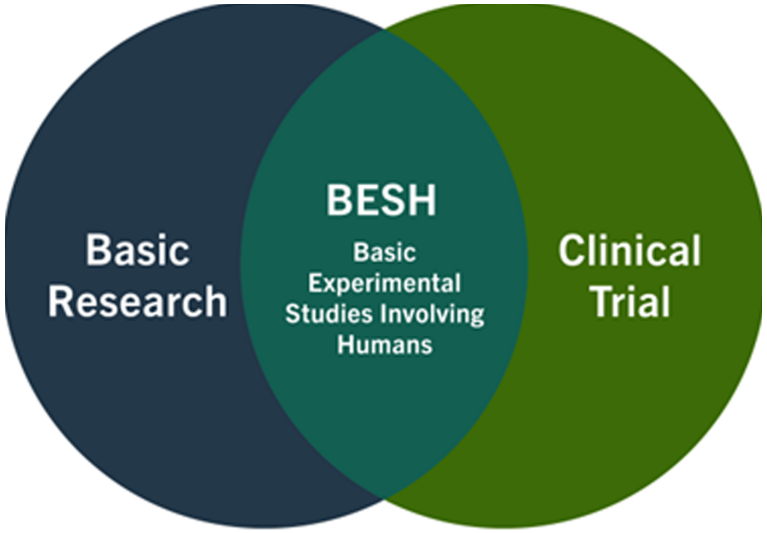
https://grants.nih.gov/policy/clinical-trials/definition.htm

“Clinical Trials Optional”

Only the following types of clinical trials will be supported:

- Mechanistic:
  The proposed study design should be designed to understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention.

- Basic Experimental Studies with Humans (BESH):
  The proposed study design should describe expected effect size and describe potential biases and/or challenges in the study design and how they will be addressed.



For more info:

- Basic Experimental Studies Involving Humans (BESH)
- Mechanistic Clinical Trials FAQs
- Does my human subjects research study meet the NIH definition of a clinical trial?

“Clinical Trials Optional” (Cont.)

This funding opportunity will not support clinical trials that seek to answer specific questions about safety, tolerability, clinical efficacy, effectiveness, clinical management, and/or implementation of pharmacologic, behavioral, biologic, surgical, or device (invasive or non-invasive) interventions.

Data Management & Sharing Plan

- All applications must submit a Data Management & Sharing (DMS) Plan that addresses the Elements as described in NOT-OD-21-014. The DMS Plan is not considered during peer review.
- For human data generated from individuals with FXS or FXTAS, data must be shared via the NIMH Data Archive (NDA).
- For human data on other FMR1-associated conditions, NICHD encourages the use of the Data and Specimen Hub (DASH).
- Applications using Common Data Elements (CDEs) should describe how standardization of data collection and data collection instruments – including the use of existing NIH CDEs – will be promoted, and how these data collection techniques will facilitate data integration or collaboration.

Resource Sharing

- The Resource Sharing Plan will be considered during peer review.
- NIH policy requires broad sharing of biomaterials collected under scientific studies. (Several NIH institutes maintain biorepositories, including the NIMH Repository and Genomics Resource, the NINDS Human Cell and Data Repository (NHCDR), and the NINDS BioSEND Repository.)
- All applications proposing to create or use tools, workflows, and/or pipelines with support from this NOFO should address how they will be shared with the wider scientific community.

RFA Nuts & Bolts

Page Limits

Available Component Types	Page Limits
Overall	12 pages
Administrative Core	6 pages
Projects (min. 2, max. 3)	12 pages per project

Center Director and Key Personnel

- Center Director(s) must devote a minimum combined total of 1.8 person-months (15%) effort to the Center
- No individual may serve as key personnel on more than one application submitted to this funding opportunity.
- NIH strongly encourages Centers to design at least one Research Project that includes an Early Stage Investigator (ESI) as key personnel
  - ESI status can be maintained if a key personnel participant acts as a co-Investigator, but not if they are one of the Principal Investigators on the overall application.
  - ESIs can also maintain their ESI status if they are the lead on a project.

Research Plan (Overall)

- Specific Aims
  - Include: identification of an overarching theme targeting at least one of the three priority research areas; explanation of how the administrative core and projects synergize to advance that theme
- Research Strategy (Selected Requirements)
  - Describe the current gaps in knowledge being addressed by the Center and its theme
  - Explain how the proposal constitutes innovations in FMR1 research
  - Describe why the research questions being asked are meaningful for People with Lived Experiences (PWLE) of FMR1 conditions
  - Describe the range of backgrounds that will be used for any subjects, animal models, or source materials/data, and justify why the distribution of backgrounds within and across projects is sufficient to address the overarching theme and specific aims

Research Plan (Administrative Core)

Applications must describe:

- Overall management and administration plans
- Experience, accomplishments, and expertise of the Administrative Core Lead and other key core personnel
- Concrete steps to be taken to ensure the core is cost-efficient
- SMART (specific, measurable, actionable, realistic, and timely) benchmarks that will be used to evaluate the success of the Administrative Core, including concrete plans for implementation and accountability
- Plans for an External Advisory Board

Budget (Administrative Core)

Allowable costs include:

- Salaries for Center Director PD(s)/PI(s) and limited administrative and clerical personnel
- Administrative support services
- Costs related to *dissemination and communication* of research results to investigators, the scientific community and lay public
- Costs related to *seminars or meetings* designed to promote interdisciplinary interaction, education, or Center cohesiveness
- Costs related to *External Advisory Board meetings*
- *Travel to one Fragile X Centers meeting annually* to confer with other Centers and program staff to promote scientific interaction
    - Will be held in the Washington, DC area

Research Plan (Project)

- Specific Aims
  - Describe specific aims for the research project
  - Describe how the proposed project will address the Center's overarching theme and specific goal areas from the *FMR1* strategic plan
- Research Strategy (RFA-specific requirements):
  - All centers **must** include at least one project that involves human subjects or large-scale human phenotypic data.
  - Any project involving animal models **must** use multiple background strains or species.

Reminder: RFA Requirements

- Applications that do not comply with the following RFA requirements **will not be considered responsive** and **will be withdrawn** from consideration:
  - Plan for Enhancing Diverse Perspectives (PEDP)
  - Administrative core and 2-3 interdependent and interrelated research projects
  - At least one project that involves human subjects or human phenotypic data
  - Clear descriptions of the range of genetic/strain backgrounds used in each project and why the distribution is sufficient to address the project objective and overall theme of the Center
  - Inclusion of **at least two** distinct levels of analysis **within one or more strains or species**
  - Plans for an External Advisory Board
- If clinical trials are proposed, they must qualify as either **mechanistic trials** or **Basic Experimental Studies in Humans (BESH)** or the application will be withdrawn.

If you're not sure – please ask!!

Potential applicants are *strongly encouraged* to consult with NIH program staff about whether their proposals will meet the requirements of this funding opportunity:

IC	Contact(s)	Email
NICHD	Melissa Parisi, M.D., Ph.D. Alice Kau, Ph.D.	parisima@mail.nih.gov kaua@mail.nih.gov
NIMH	Lisa Gilotty, Ph.D.	gilottyl@mail.nih.gov
NINDS	Robert Riddle, Ph.D.	riddler@nih.gov
NIDCD	Holly Storkel, Ph.D.	holly.storkel@nih.gov

Just a reminder…

- This RFA is not the only mechanism for NIH support of *FMR1*-related research

- We welcome proposals addressing all aspects of the NIH *FMR1* Strategic Plan through investigator-initiated mechanisms and other relevant funding opportunities.

Frequently Asked Questions (FAQs)

FAQs

Question	Response
Are centers required to address more than one *FMR1*-associated condition?	No. Such applications are allowed, but this is not a requirement.
Are multi-institution proposals allowed?	Yes. Such collaborations are not required but are allowed if they are likely to increase synergy between projects and/or provide the required expertise to meet the requirements of the RFA.
How many awards will be made?	NICHD and partnering institutes intend to commit an estimated total of $5.45 million for this funding opportunity to fund three awards.
How much funding can be requested?	Applications may request up to $1.2 million in direct costs per year, excluding subaward facilities and administrative costs. This request must reflect the actual needs of the proposed projects.

Other questions?