Informational Pre-Submission Webinar: Centers for Collaborative Research in Fragile X and *FMR1*-Associated Conditions (P50 Clinical Trial Optional)

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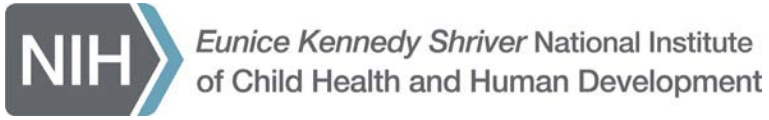
February 18, 2020 | 3:00 pm – 4:00 pm EST



Webinar Basics

- All participants are being muted on entry
- Please type your questions into the “Chat” box – we will have a Q&A session at the end of the prepared presentation
  - We will unmute participants during the Q&A session. If you attempt to speak and are not being heard, you may need to both unmute your phone and unmute yourself in the WebEx platform.
- If you have questions that do not get answered during this session, please submit them by email to tracy.king@nih.gov.
- We will be posting these slides, the recording of this webinar, and FAQ’s on the website for the Intellectual and Developmental Disabilities Branch at NICHD: https://www.nichd.nih.gov/about/org/der/branches/iddb

Outline

- Background: 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-20-003)
- Q&A

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

- 2-year process
- Substantial input from researchers, advocacy organizations, federal funding agencies
  - Included 2 rounds of public input
- Goals for specific *FMR1*-associated conditions
- Cross-cutting themes

Long-Term Vision: Effective prevention and treatment interventions for *FMR1*-associated conditions

- Recognition that this will require progress across the translational spectrum
  - Basic genetic / molecular biology research
  - Studies in animal models
  - Clinical trials
  - Implementation research
- No inherent priority or ranking of goals
- Recognition that levels of current knowledge vary across conditions

Fragile X Syndrome (FXS)

- Goal 1.1: Identify novel mechanisms and targets for intervention
- Goal 1.2: Develop and refine etiologically and physiologically relevant models
- Goal 1.3: Develop and validate biomarkers and outcome measures
- Goal 1.4: Characterize human phenotypes and risk factors across the lifespan
- Goal 1.5: Assess the safety and effectiveness of prevention and treatment interventions
- Goal 1.6: Extend outreach, particularly to groups underrepresented in FXS research

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

- Goal 2.1: Describe pathogenic mechanisms underlying FXTAS
- Goal 2.2: Develop precise, easily measurable diagnostic criteria
- Goal 2.3: Develop and validate biomarkers and outcome measures
- Goal 2.4: Characterize human phenotypes and risk factors across the lifespan
- Goal 2.5: Assess safety and effectiveness of prevention and treatment interventions
- Goal 2.6: Extend outreach to the community

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

- Goal 3.1: Identify the mechanisms leading to ovarian dysfunction
- Goal 3.2: Develop biomarkers to facilitate early diagnosis and risk stratification
- Goal 3.3: Extend outreach to the community

FMR1 Premutations

- Goal 4.1: Understand the stability of the premutation
- Goal 4.2: Develop technologies for carrier testing and premutation screening
- Goal 4.3: Characterize premutation-associated conditions and risk factors

Cross-Cutting Issues

- Infrastructure, Research Training, and Career Development
- Promoting Collaborations Between Basic Scientists and Clinicians
- Ethical, Legal, and Social Issues in Premutation Screening and Testing

Current Funding Opportunity

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

RFA-HD-20-003

The Basics

- Submission Deadline: April 3, 2020
  - Letters of Intent requested by March 4, 2020 (30 days prior to deadline)
- Budget Limit: $1.3M/year direct costs
- Anticipated number of awards: 3-4
  - 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, NCATS

Key Principles

Specific Areas of Research Interest

Requirement: Multiple Levels of Analysis

Justify Use of Center Mechanism

“Clinical Trials Optional” – What does that mean in this RFA?

Requirement: Resource Sharing

Purpose

- Mechanism for addressing 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 3 priority research areas drawn from the *FMR1* Strategic Plan:
  - Identify novel mechanisms and targets for intervention across models of FMR1-associated conditions
  - Develop and validate biomarkers that translate across human and animal models
  - Characterize phenotypes of *FMR1*-associated conditions and risk factors for disease severity across developmental stages and diverse populations
- Applications that do not address one or more of these priority research areas will not be considered responsive to this funding opportunity.

Priority area 1: Identify novel mechanisms and targets for intervention

- Characterize genetic and epigenetic mechanisms that underlie *FMR1*-associated conditions, including
  - the stability/instability of CGG repeats and potential modifiers of repeat expansions
  - the role of repeat-associated non-AUG (RAN) translation in the pathophysiology of premutation conditions
- Characterize brain circuit/network-level mechanisms that underlie key features of human phenotypes and may be amenable to therapeutic interventions
- Such studies may require development and validation of cellular and animal models that more closely mimic the genetics, physiology, phenotypes and development of *FMR1*-associated conditions in humans.

Priority area 2: Develop and validate biomarkers that translate across human and animal models

- Conduct concomitant, iterative studies of biomarkers that are conserved across human and animal models of *FMR1*-associated conditions and thus have the potential to accelerate bidirectional translation of discoveries.
- Research addressing this priority area must include both animal studies and preliminary human validation research using carefully standardized human samples or human clinical studies.

Priority area 3: Characterize phenotypes of *FMR1*-associated conditions and risk factors for disease severity across developmental stages and diverse populations

- Conduct natural history studies to characterize the evolution of phenotypes over time, and identify genetic and environmental influences upon key phenotypes
- In the case of premutation conditions, such natural history studies may require validation of diagnostic criteria to facilitate accurate and timely identification of affected individuals
- Any such efforts must include individuals from diverse racial, ethnic and socioeconomic backgrounds

Requirement: Multiple Levels of Analysis

- Centers must propose hypothesis-driven projects, as appropriate, that include at least two distinct levels of analysis within one or more species.

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
- Projects involving brain/behavioral outcomes must include human subjects or human materials (e.g. human tissues, human-derived cell lines) as one of the species being studied.

Requirement: Multiple Levels of Analysis (Cont.)

- Studies involving reproductive outcomes should choose at least two from among the following levels of analysis:
  - genomic/molecular measures
  - endocrine measures
  - tissue specific and/or cell-type specific measures
  - clinical/whole organism measures

Requirement: Multiple Levels of Analysis (Cont.)

- 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

Justify Use of Center Mechanism

- Describe 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.

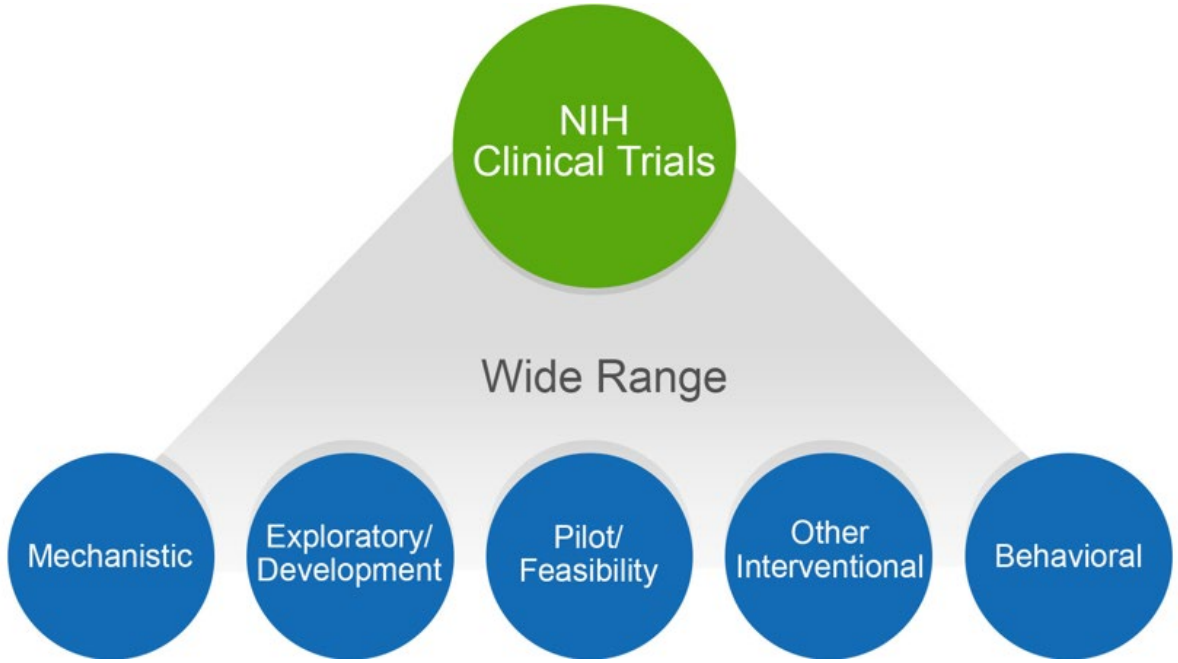
How Does NIH Define a Clinical Trial?

*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”

- Encompasses a wide range of types of trials, including:
  - Mechanistic
  - Exploratory
  - Pilot/Feasibility
  - Behavioral
- With broader definition, many more studies are now classified as clinical trials



“Clinical Trials Optional” (Cont.)

- Any clinical trials proposed as part of a Fragile X Center must be *mechanistic* or *early stage proof-of-concept* trials.
- Should be designed to provide insight into the biological or behavioral processes underlying *FMR1*-associated conditions or provide specific data necessary to design a subsequent definitive efficacy trial.

“Clinical Trials Optional” (Cont.)

- Examples of relevant clinical trials or studies:
  - Studies aimed at elucidating potential mechanisms by which interventions act to modify outcomes of interest
  - Studies designed to evaluate whether an intervention produces sufficient evidence of short-term activity (e.g., biomarker activity) in humans to justify an efficacy trial
  - Studies to identify inclusion and exclusion criteria to be applied in a subsequent efficacy trial
- Should be strong evidence of the potential value and feasibility
  - Clear preclinical rationale (if applicable)
  - Unimpaired regulatory status
  - Evidence of drug/biologic availability for use in a trial
  - Agreement of all participating clinical/corporate partners

“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 interventions
  - Includes pharmacologic, behavioral, biologic, surgical, or device (invasive or non-invasive) interventions, preventive, therapeutic, and services interventions.

Requirement: Resource Sharing

- Applicants must describe plans, including a timeline, for making data and key biological resources publicly available.
- Should also include the sharing of other resources (e.g., research tools and key reagents, analytic software code).
  - Projects on FXS involving human subjects will be required to contribute data to NIMH Data Archive (NDA)
    - formerly the National Database for Autism Research (NDAR)
  - Projects studying neurological outcomes and collecting biospecimens are strongly encouraged to use the NINDS Biomarkers Repository
    - BioSpecimen Exchange for Neurological Disorders (BioSEND)

Requirement: Resource Sharing (Cont.)

- The degree to which a proposed Resource Sharing Plan is appropriate and consistent with the goals of the NIH Fragile X Centers program will be considered during peer review and by program staff as award decisions are being made.

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
- Center Directors(s) cannot serve as the Lead of a core or research project on another active Fragile X Center
  - Not prohibited from serving as a co-investigator on another Center if not Core Lead or Project Lead
- Key Personnel
  - Applicants are expected to integrate junior faculty-level investigators within the structure of the Center.

Overall: Research Strategy

- Purpose of the Program
- Administrative Structure
  - Describe organizational framework
  - Provide an organizational chart for the overall Center, including the Administrative Core and all Research Projects.
- Description of Assurances and Collaborative Agreements
  - Provide an overview and rationale for any collaborative and cooperative endeavors or subcontracts

Overall: Research Strategy (Cont.)

- Research Program that highlights central theme of Center
  - Strategy for achieving Center's goals, how each research project relates to that strategy
  - Center should be viewed as interrelated research projects, each of which is not only individually meritorious but is also complementary to the other projects and related to the overall theme of the Center.
  - Describe how the proposed research will contribute to NIH long-term vision of developing effective prevention and treatment interventions for *FMR1*-associated conditions.
  - Priority areas, levels of analyses, and species being studied must be explicitly identified

Administrative Core: Research Strategy

- Purpose
- Organizational structure and staffing
- Services provided to Center Research Projects
- Management plan
  - contractual agreements
  - resource sharing activities
  - publication plans
- Plans for communicating and collaborating with other NIH-funded Fragile X Centers wherever possible

Administrative Core: Research Strategy (Cont.)

- Dissemination and Outreach efforts
  - Should occur at all stages of research
    - Identification of key study outcomes
    - Recruitment of study participants
    - Dissemination of research findings
- External Advisory Committee
  - Must include external scientific and lay members
    - Describe the types of individuals who will be appointed
    - Specific individuals should not be named or contacted
- Evaluation Plan
  - Center activities should be evaluated at least annually
  - Should include specific steps for reporting and responding to evaluation findings.

Administrative Core: Budget

Allowable costs include:

- 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 Committee 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 Project: Research Strategy

- Describe relationship of the Project to overall theme of the Center and interactions with other Research Projects
  - Describe how collaborations between projects and investigators are expected to yield results *beyond those achievable if each project were pursued separately* and without formal interaction among investigators
- For any project that involves preclinical research, describe what measures will be taken to assure *adequate rigor*
  - experimental design
  - minimizing bias
  - interpretation of results
  - transparency of reporting

Reminder: “Clinical Trials Optional” (Cont.)

- Any clinical trials proposed as part of a Fragile X Center must be *mechanistic* or *early stage proof-of-concept* trials.
- Should be designed to provide insight into the biological or behavioral processes underlying *FMR1*-associated conditions or provide specific data necessary to design a subsequent definitive efficacy trial.

Reminder: "Clinical Trials Optional" (Cont.)

- Examples of relevant clinical trials or studies:
  - Studies aimed at elucidating potential mechanisms by which interventions act to modify outcomes of interest
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Reminder: Resource Sharing is Required

- Applicants must describe plans, including a timeline, for making data and key biological resources publicly available.
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Reminder: Resource Sharing is Required (Cont.)

- The degree to which a proposed Resource Sharing Plan is appropriate and consistent with the goals of the NIH Fragile X Centers program will be considered during peer review and by program staff as award decisions are being made.

Review Criteria

Review Criteria: Overall

- Overall score will emphasize the *interrelatedness* and *synergy* among the proposed research projects
  - meaningful and committed interactions among projects and disciplines
  - sharing of materials, results, data, patient populations, or methodologies between projects as appropriate
  - integration around a common unifying theme
- Potential for Center as a whole to have a significant impact on the field during the term of the award
  - weighing balance of more conventional approaches with highly innovative components or projects in which success is not guaranteed

Review Criteria: Overall (Cont.)

- Integration or “centeredness” of the overall program
  - *Does the program function as a true “Center”* rather than a collection of individual research projects, with the sum of the parts being greater than the individual components?
  - To what extent will proposed *communication, coordination and collaboration* efforts between Center components, with other Centers, and among key stakeholders *accelerate the Center's progress*?
  - *Is value added* by having the proposed Research Projects comprise a Center that can leverage additional resources that would not have been possible without an integrated Center structure?
  - Is the Center *multidisciplinary* in scope and does it have the ability to catalyze significant research advances in *FMR1*-associated research?
  - Is a *dissemination plan integrated with the scientific goals* of the Center and likely to facilitate communication among stakeholders, including families affected by *FMR1*-associated conditions?

Review Criteria: Administrative Core

- Reviewers will assign an impact score to the Administrative Core based on the following review criteria:
  - How well does the Administrative Core fit into the central theme of the Center?
  - Does the proposed Core Director have adequate experience in the administration of large research centers?
  - Does the application clearly describe and justify the proposed Administrative Core operational plan and organizational structure?
  - Does the application describe adequate plans for management of day-to-day program activities?

Review Criteria: Administrative Core (Cont.)

- Reviewers will assign an impact score to the Administrative Core based on the following review criteria: (continued)
  - Does the application adequately describe plans for implementation of the Resource Sharing Plan?
  - Does the application include adequate provisions for dissemination and outreach efforts to support all stages of the proposed research and to share study progress with relevant stakeholders?
    - Where appropriate, do these plans include strategies for communicating information to diverse populations, including non-English-speaking people and racial and ethnic minorities?
  - Does the application include an appropriate plan for program evaluation, including convening an External Advisory Committee (EAC) with appropriate scientific and lay expertise, and specific procedures for acting upon evaluation findings and EAC recommendations?

Reminder: RFA Requirements

- Applications that do not comply with the following RFA requirements **will not be considered responsive** and **will be withdrawn** from consideration
  - Addressing one or more of the three *identified* priority areas
  - Utilizing *at least two levels of analysis* in one or more species
    - Projects involving *brain/behavioral outcomes must include human subjects or human materials* (e.g. human tissues, human-derived cell lines) as one of the species being studied
  - *For biomarker studies:* Inclusion of *both* animal studies and human validation research
  - Any proposed clinical trial *must be a mechanistic or early stage proof-of-concept* trial
    - Efficacy / effectiveness trials are <u>not</u> allowed under this funding opportunity
  - *Required:* resource sharing plan

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:

Institute	Person	Email
NICHD	Tracy King, M.D., M.P.H.	tracy.king@nih.gov
NIMH	Bettina Buhring, Ph.D. Lisa Gilotty, Ph.D.	bettina.buhring@nih.gov gilottyl@mail.nih.gov
NINDS	Laura Mamounas, Ph.D.	mamounal@ninds.nih.gov
NCATS	Tiina K. Urv, Ph.D.	urvtiin@mail.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
(as of 2/17/20)

FAQ's (to date)

Question	Response
Are Centers required to address more than one *FMR1*-associated condition?	No. Such applications are welcome, but this is not a requirement.
Are multi-institution proposals allowed?	Yes. Such collaborations are encouraged, particularly if they provide the expertise needed to meet the requirements of the RFA.
So studies of brain/behavioral outcomes cannot be comprised only of mouse studies?	Correct. Studies of brain/behavioral outcomes can include mouse or other animal studies, but must also include human subjects or human materials.
The *FMR1* strategic plan discusses the importance of understanding sex differences…but I don't see specific language about this in the RFA?	Yes, this is certainly an area of interest. We intended this to be captured under the following priority area: • Characterize phenotypes of *FMR1*-associated conditions and risk factors for disease severity across developmental stages and diverse populations

FAQ's (to date)

Question	Response
Are human iPSC's allowed? Do they meet the requirement for human studies?	Yes, they are allowed, and yes, they meet the requirement for studies of human materials.
Are there requirements for which specific hiPSC lines can be used?	There is no requirement for use of specific existing cell lines. Any hiPSCs used should meet the RFA requirements for rigor of design, conduct, analysis and results reporting, as well as NIH-wide requirements for rigor and reproducibility of research.
Are we required to include more than one species for mechanistic projects?	Projects addressing the priority area of *developing and validating biomarkers* must include both animal studies and studies of human subjects or human materials. For projects addressing other priority areas, inclusion of multiple species is encouraged but not required.

FAQ’s (to date)

Question	Response
I am an appointed study section member with continuous submission privileges. Does that apply to this RFA?	No. Continuous submission only applies to R01s, R21s and R34s submitted to FOAs using standard due dates. This RFA does not use any of these mechanisms and does not use standard due dates: therefore, applications are not eligible for continuous submission.
I recently submitted an R01 on FXS. Can I include any part of that project in a Center application?	No. NIH policy states that you cannot have duplicate or highly overlapping applications under review at the same time. (An application is considered “under review” until the summary statement is issued.)

Other questions?

tracy.king@nih.gov

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