Pre-Application Webinar for RFA-TR-21-008

Multi-disciplinary Machine-assisted, Genomic Analysis and Clinical Approaches to Shortening the Rare Diseases Diagnostic Odyssey (UG3/UH3 Clinical Trial Optional)

March 12, 2021

We will start at 3:05 p.m. EST

**Webinar will be recorded**
Webinar Logistics: Webex Events

• The webinar will be **recorded** for note-taking purposes
  • The recording will **not** be posted afterward

• The slide deck will be available on the NCATS Events webpage: https://ncats.nih.gov/events/RFA-TR-21-008

• All attendees are muted on entry
  • If you have questions, please type them into the “Q&A” box or “raise hand,” and we will respond during the question-and-answer period

• Responses to questions will also be posted: https://ncats.nih.gov/events/RFA-TR-21-008
Webinar Objectives

• To provide orientation and technical assistance to potential applicants by explaining the goals and objectives of funding opportunity announcement (FOA), RFA-TR-21-008
• To answer questions from webinar attendees
Key Dates

- **FOA posted**: January 15, 2021
- **Pre-application webinar**: March 12, 2021
- **Earliest submission date**: March 19, 2021
- **Letter of intent due**: 30 days prior to application due date
- **Application due date**: April 19, 2021 (by 5:00 PM local time of applicant organization)
- **Scientific Merit review**: July 2021
- **Advisory Council review**: October 2021
- **Earliest start date**: December 2021
Section I: Purpose and Background

- Most rare disease patients experience years-long delays and often need to consult with multiple physicians and specialists before obtaining a correct diagnosis.

- Delays in obtaining a correct diagnosis lead to several problems for rare disease patients, such as redundant testing and procedures, misdiagnosis which may lead to inappropriate treatment, and importantly, substantial delays in obtaining disease-appropriate management and treatment.

- Many front-line clinicians may have no prior experience with individual rare diseases, which contributes to the difficulty in diagnosis, and often requires specialist, sub-specialist, or multi-disciplinary referral to accurately diagnose the patient.
Section I: Purpose and Background (cont.)

• This FOA is seeking diagnostic strategies incorporating clinical consultation, machine-assistance, and genomic analyses that could provide more rapid identification, escalation, and accurate diagnosis of hard-to-diagnose patients.

• Multi-disciplinary strategies must be able to be adopted and performed at the primary or secondary care levels by front-line healthcare providers and be readily integrated into their clinical care workflow.
Section I: Research Objectives and Scope

• To promote the planning and development of multi-disciplinary rare disease diagnostic strategies that will rapidly identify and escalate hard-to-diagnose or undiagnosed patients

• Diagnostic strategies must:
  • Be applicable to a broad array of rare diseases
  • Integrate machine-assistance strategies, rapid genomic analysis or interpretation of a laboratory testing panel, and clinical consultation within the project
Examples of approaches that could be incorporated into a diagnostic strategy include, but are not limited to:

- **Clinical strategies**
  - Creation of a multi-disciplinary expert diagnostic team
  - Creation of a framework through which front-line providers can rapidly escalate hard-to-diagnose patients

- **Machine-assistance**
  - Development of disease-agnostic algorithms to identify hard-to-diagnose patients through electronic medical records or other healthcare system databases
  - Use of facial recognition or augmented reality software in the diagnostic process
  - Development of a strategy to seamlessly integrate machine-assistance into the diagnostic process, such as through machine-alerts to clinicians

- **Genomic analysis**
  - Creation of a framework through which rapid genomic analysis will be obtained and interpreted
  - Identification of clusters of related disorders that could be escalated to laboratory/genetic panel-testing
Section II: Funding Instrument

• Cooperative Agreement:
  • A support mechanism used when there will be substantial Federal scientific or programmatic involvement
  • Substantial involvement means that, after award, NIH scientific or program staff will assist, guide, coordinate, or participate in project activities
  • See Section VI.2 for additional information about the substantial involvement for this FOA
  • Cooperative Agreement Terms and Conditions of Award
Section II: Award Project Period and Budget

**UG3 Phase:** To develop an innovative diagnostic strategy and pilot test the strategy at a single front-line healthcare setting
- Major goal is on **planning** and **developing** a diagnostic process for rare diseases, and **pilot testing** of critical experimental parameters in a **single** front-line healthcare setting

**UH3 Phase:** To assess the feasibility of disseminating the diagnostic strategy into at least one other clinical setting
- Major goal is to **disseminate** the diagnostic strategy into at least one **other** clinical care setting, and identify and overcome **challenges** to doing so

- **UG3:** $200K direct costs per year
- **UH3:** $300K direct costs per year

**UG3/UH3 Transition:**
- Administrative review by NIH
- Based on negotiated milestones
  - Have clear, testable components for each of the 3 required areas (clinical, machine-assistance, genomic analysis)
  - Use **quantifiable measures** for making a go/no-go decision to progress to clinical testing
Section IV: Research Plan

• Specific Aims (1-page limit):
  • Provide the overall goals or hypotheses for the entire project period
  • Identify separate specific aims to be accomplished in the UG3 phase and in the UH3 phase

• Research Strategy (12-page limit):
  • Must provide separate sections that describe both the UG3 and UH3 phases
  • Must include diagnostic strategies applicable to a broad array of rare diseases that integrate machine-assistance, genomic analysis or laboratory panel testing, and clinical consultation that can be adopted or performed by front-line healthcare providers
Section IV: Research Plan (cont.)

• Transition Milestones (for transition from the UG3 Phase to the UH3 Phase)
  • Must include **clearly identified milestones** for completion of the UG3 phase and transition to the UH3 phase for up to 3 years of **additional** funding
  • A timeline (**Gantt chart**) including milestones required for all components of the diagnostic strategy
    • **Quantitative** milestones are required in order to provide clear indicators of a project's continued success or emergent difficulties
• The milestones and timeline for each stage must be provided in a separate heading at the end of the approach section for the UG3 and the UH3 component and include the following:
  • Detailed **quantitative** criteria by which milestone achievement will be assessed
  • Detailed **timeline** for the anticipated attainment of each milestone and the overall goal
Section IV: Resource Sharing Plan

• All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan
Section V: Scored Review Criteria —Specific to this FOA

• Significance
  • To what extent will the outcomes of the proposed diagnostic strategy represent a substantial advance over available approaches for hard-to-diagnose patients? How will successful completion of the aims change the methods for adoption of coordinated diagnostic strategies into clinical practice for suspected rare disease patients across the rare disease field?

• Investigator(s)
  • How strong is the rare disease, genomics, informatics, and front-line healthcare research expertise of the PD(s)/PI(s) and Key Personnel involved in the multi-disciplinary diagnostic approach? Is there strong evidence that the PD/PI has experience leading a multi-disciplinary team and managing administrative functions? Is the Multi-PI leadership plan, if applicable, well-described, including plans for dispute resolution? Have project leadership and other key personnel demonstrated a record of directing research activities related to creating and validating the individual components of the diagnostic strategy within their areas of expertise?
Section V: Scored Review Criteria —Specific to this FOA (cont.)

• Innovation
  • How strong is the justification/rationale provided that the diagnostic strategy is applicable to a broad array of rare diseases? How strong is the justification/rationale provided that the diagnostic strategy seeks to shift current research or clinical practice paradigms by utilizing multi-disciplinary and coordinated approaches to rare disease diagnosis, including machine-assistance, genomics/laboratory panel analyses, and clinical consultation?

• Environment
  • To what extent does the UG3 phase of the application provide for integration of the diagnostic strategy into a front-line healthcare setting? To what extent does the application propose sites to be chosen for the UH3 phase representing diverse clinical care settings?
Section V: Scored Review Criteria
—In addition, for applications involving clinical trials

• Under each of the review criteria:
  • Significance
  • Investigator(s)
  • Innovation
  • Approach
  • Environment
Scientific Merit Review
Section V: Review and Selection Process

• Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by NCATS, in accordance with NIH peer review policy and procedures, using the stated review criteria.

• Following initial peer review, recommended applications will receive a second level of review by the NCATS Advisory Council.

• The following will be considered in making funding decisions:
  • Scientific and technical merit of the proposed project as determined by scientific peer review.
  • Availability of funds.
  • Relevance of the proposed project to program priorities.
Suggestions!

1. **READ THE FOA!!!!!!**
   - Keep in mind the goals and objectives as described in the “Funding Opportunity Purpose” on the first page and in Section I. Funding Opportunity Description. Ask yourself, “Will my project help to achieve these goals?”
   - **FOLLOW THE INSTRUCTIONS!**

2. As you assemble your application (Which you will do early, won’t you?) follow the instructions in Section IV. Application and Submission Information.
Suggestions!

3. As you finish an early draft, look again at Section V. Application Review Information

• These are the review criteria that scientific review staff will assure panel members use to evaluate your application. Every application is evaluated on basis of the same criteria.

• These questions are to guide reviewers in their evaluations. Ask yourself how favorably reviewers will respond to the questions in this section as they read your application. As you revise and polish your application towards the final version for submission, think in terms of eliciting favorable/enthusiastic responses from reviewers.
4. As you are approaching “final version,” step back, take a 30,000 ft view, and ask yourself again — Will my project be a significant contribution towards reaching the goals as stated in the Funding Opportunity Purpose?

- Does my application meet the “spirit” of the FOA as laid out in Section I. Funding Opportunity Description?
  - e.g., Maybe you need to lay out the rationale more clearly in the Abstract or beginning of the Research Strategy.

Importantly, you want your application to stand out as exceptionally good — conceptually, scientifically/technically, and in terms of potential impact.
An Important Note
Helpful NIH Resources about Clinical Trials

• This is a reissue of RFA-TR-20-030: Multi-disciplinary Machine-assisted, Genomic Analysis and Clinical Approaches to Shortening the Rare Diseases Diagnostic Odyssey (UG3/UH3 Clinical Trial Not Allowed)

• A Notice of Termination of RFA-TR-20-030 (NOT-TR-21-018) was released on January 25, 2021

• NIH Definition of a Clinical Trial:
  • https://grants.nih.gov/ct-decision/index.htm
  • https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm#ClinicalTrial

• NIH Definition of Clinical Trial Case Studies:
  • https://grants.nih.gov/policy/clinical-trials/case-studies.htm
  • https://grants.nih.gov/policy/clinical-trials/CT-Definition-Case-Studies_1.7.19.pdf
NIH Clinical Trial Case Studies

Case #20: The study involves the recruitment of healthcare providers to assess the extent to which being provided with genomic sequence information about their patients informs their treatment of those patients towards improved outcomes.

- Does the study involve human participants? Yes, both the physicians and the patients are human participants.
- Are the participants prospectively assigned to an intervention? Yes, physicians are prospectively assigned to receive genomic sequence information, which is the intervention.
- Is the study designed to evaluate the effect of the intervention on the participants? Yes, the study is designed to evaluate the effect of intervening with physicians, on the treatment they provide to their patients.
- Is the effect being evaluated a health-related, biomedical, or behavioral outcome? Yes, the effect being evaluated, the extent to which providing specific information to physicians informs the treatment of patients, is a health-related outcome.

This study is a clinical trial.

Keyword(s): Clinical Care;

Case #17: Disease X to be evaluated with a new executive function task. It is designed to evaluate the ability of the new task to measure executive function.

- Does the study involve human participants? Yes, the study involves human participants.
- Are the participants prospectively assigned to an intervention? Yes, the participants are prospectively assigned to an intervention, the executive function task.
- Is the study designed to evaluate the effect of the intervention on the participants? No, the study is designed to evaluate the ability of the executive function task to measure executive function (as measured by the current standard instrument), but not to modify it.

This study is not a clinical trial.

Keyword(s): Behavioral

NIH Clinical Trial Case Studies (cont.)

Case #8a: The study involves the recruitment of research participants with disease X. It is designed to compare the diagnostic performance of approved devices A and B, both of which are used in clinical practice, to measure disease markers. Device A will be used in half of the patients; device B will be used in the other half.

- Does the study involve human participants? Yes, the study involves human participants.
- Are the participants prospectively assigned to an intervention? No, in this context the diagnostic device would not be considered an intervention. The purpose of the study is to evaluate the diagnostic performance of two devices, but not to determine their effects on any health-related or behavioral outcomes.

X This study is not a clinical trial.

Keyword(s): Device

Case #8b: The study involves the recruitment of research participants suspected to have disease X. It is designed to compare the ability of approved devices A and B to diagnose the disease and inform the clinical management of disease X. Device A will be used in half of the patients; device B will be used in the other half.

- Does the study involve human participants? Yes, the study involves human participants.
- Are the participants prospectively assigned to an intervention? Yes, the participants are prospectively assigned to receive an intervention, one of two diagnostic devices.
- Is the study designed to evaluate the effect of the intervention on the participants? Yes, the study is designed to evaluate the ability of the two approved devices to inform the clinical management of disease X.
- Is the effect being evaluated a health-related biomedical or behavioral outcome? Yes, the effect being evaluated, diagnosis and clinical management of patients with disease X is a health-related outcome.

✓ This study is a clinical trial.

Keyword(s): Device; Clinical Care

Case #8c: The study involves the recruitment of research participants suspected to have disease X. It is designed to compare the ability of commercial sensors A and B to improve diagnosis of the disease and inform the management of clinical outcomes. Device A will be used in half of the patients; device B will be used in the other half.

- Does the study involve human participants? Yes, the study involves human participants.
- Are the participants prospectively assigned to an intervention? Yes, the participants are prospectively assigned to receive an intervention, one of two diagnostic devices.
- Is the study designed to evaluate the effect of the intervention on the participants? Yes, the study is designed to evaluate the ability of the two commercially available devices to diagnose disease X, and in that way to inform diagnosis and clinical management.
- Is the effect being evaluated a health-related biomedical or behavioral outcome? Yes, the effect being evaluated, diagnosis and clinical management of patients with disease X is a health-related outcome.

✓ This study is a clinical trial.

Keyword(s): Device; Clinical Care
Summary about Clinical Trials

• In general, our interpretation of the guidance is:
  • Studies to evaluate operating characteristics of a test, device, or software (e.g., accuracy, sensitivity, specificity) *per se* are not clinical trials
  • Studies to evaluate the effect of a test, device, or software on patients or care processes are clinical trials

• NCATS Chief Medical Officer
  • Sam Bozzette, MD, PhD
  • Email: sam.bozzette@nih.gov
Frequently Asked Questions
Q: What is considered a “broad” array of rare diseases?

• A: Strategies focused on the identification of a single disease or a narrow subgroup of rare diseases will be considered non-responsive. Clusters of related diseases, such as generalized seizures or motor impairment, would be responsive because they involve multiple rare diseases.

• A: The intent of the FOA is to identify, escalate, and accurately diagnose as many rare disease patients who are hard-to-diagnose as possible. A diagnostic strategy that applies to multiple disorders will be most suitable.
  • Example: Machine-assisted algorithms using clinical characteristics or disease-specific attributes to identify patients with one rare disease would not be considered responsive.
  • Example: Augmented reality software to analyze gait abnormalities, applicable to multiple neuromuscular diseases, would be considered responsive.
Q: What is considered a “multi-disciplinary” team?

A: In view of the goals of this FOA, applicants should assemble a multi-disciplinary team with expertise in medical informatics, genetic analysis, rare diseases, and front-line healthcare when preparing the application.
Q: What are some key elements to consider in an application for this UG3/UH3 activity code?

• A: The transition plan with clear \textit{go/no-go criteria} and meeting the UG3 milestones are crucial to continued funding to the UH3 phase. NIH can consider ending support and negotiating an orderly close-out of the award if at any time the project fails to make progress toward meeting milestones.

• A: Establish a robust milestone plan with clear \textit{quantifiable} measures of success. A timeline (Gantt chart) including milestones is required for all components of the diagnostic strategy.
  • Quantitative milestones are \textit{required} in order to provide clear indicators of a project's continued success or emergent difficulties and will be used to evaluate consideration of the awarded project for funding of non-competing award years.
Q: Given the amount of the award budget, what should be accomplished in the UG3 phase?

• A: The primary focus of the UG3 phase should be on planning and developing a diagnostic process for rare diseases.

• A: Pilot testing of critical experimental parameters in a single front-line healthcare setting should also be evaluated with quantifiable outcome measures.
Q: For the UH3 phase, what is considered another clinical setting?

- A: The UH3 phase is intended to expand the diagnostic strategy beyond the initial front-line healthcare setting so it is not too customized for any one clinical setting. This requirement will assess the feasibility of disseminating to and working for more patients, as well as adaptability by front-line healthcare providers in more than one setting.
  - Examples include, but are not limited to:
    - Affiliate community sites
    - Satellite primary care clinics
    - Local secondary care specialists
  - A: Ideally, this would include clinical care settings which reflect health disparities, and which differ with regard to demographic, geographic (e.g., rural versus urban), and socioeconomic factors.
Q: What is the role of the front-line healthcare provider?

A: Front-line healthcare providers are more likely to interact with rare disease patients earlier in their diagnostic journey. The intent of this FOA is to integrate better diagnostic strategies into the clinical care workflow of front-line healthcare providers in order to more rapidly identify, escalate, and accurately diagnose these patients.

For example, is there a way for front-line clinicians to more easily leverage assistance for suspected rare disease patients, or can front-line clinicians’ awareness of a rare disease as a possible diagnosis be incorporated into patient evaluation? It is not expected that front-line healthcare providers would be required to order, complete, or interpret genomic analyses themselves.

The FOA allows for flexibility; it is up to the multi-disciplinary team to determine how best to incorporate each of the 3 required areas into the overall proposal and fit the strategies into the workflow of front-line healthcare providers.
Q: Do "front-line" providers need to be primary care providers? Could hospital-based providers (e.g., hospitalists, intensive care clinicians) be considered front-line?

• A: Secondary care levels may also be considered front-line healthcare providers. The intent of the FOA is to accelerate diagnosis by reaching the front-line healthcare providers who see a broad array of patients in the community.

• A: It is possible to put together a proposal including hospital-based providers as long as the primary intent of the FOA is met.
Q: Does using commercially available genetic testing options count sufficiently towards the genomic analysis component?

• A: It is up to the PI to make the case.
Q: Can you elaborate on the machine-assistance aspect of the FOA?

• A: Artificial intelligence, including machine learning or other information technology (IT), components of the project may include:
  • Development of algorithms that computationally make predictions based on data
    • May be applied to the EMR or other healthcare system databases, genomic data, imaging data, and other biological domains
  • Knowledge extraction, such as natural language processing
  • Machine capture and interpretation, such as facial recognition

• A: The goal would be to develop and apply algorithms that could identify potential rare disease patients on the basis of, for example:
  • Medical utilization patterns (e.g., high-utilizers, young age)
  • Sentinel characteristics or other features (e.g., abnormal gait, facial features, delayed development)
  • Imprecise diagnosis (e.g., neurologic disorder not otherwise specified, failure to thrive)
  • Clusters of diseases that are related in some way (e.g., generalized seizures, motor impairment)
Q: Could activities of this type fall under the definition of a clinical trial?

• A: The NIH definition of a clinical trial encompasses a broad range of studies, including research studies in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

• A: Refer to the SF424 (R&R) Application Guide: R.500 – PHS Human Subjects and Clinical Trials Information; 1.4 Clinical Trial Questionnaire.

• A: See also the NIH Definition of Clinical Trial Case Studies here: https://grants.nih.gov/policy/clinical-trials.case-studies.htm.
Section VII: Agency Contacts

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