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Pre-Application Webinar for 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)

October 6, 2020

We will start at 3:05 ET

Webinar will be recorded

National Center for Advancing Translational Sciences

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#pre-application-webinar-RFA-TR-20-030
- 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
- A list of “Frequently Asked Questions” will be posted on: https://ncats.nih.gov/events#pre-application-webinar-RFA-TR-20-030

Webinar Objectives

- To provide orientation and technical assistance to potential applicants by explaining the goals and objectives of funding opportunity announcement (FOA), RFA-TR-20-030
- To answer questions from webinar attendees

Key Dates

- RFA posted: August 28, 2020
- Pre-application webinar: October 6, 2020
- Earliest submission date: October 12, 2020
- Letter of intent due: 30 days prior to application due date
- Application due date: November 12, 2020 (by 5:00 PM local time of applicant organization)
- Scientific Review: January 2021
- Advisory Council: May 2021
- Earliest start date: July 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

Section I: Research Objectives and Scope (cont.)

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 primary care 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 primary care setting

- Major goal is on **planning** and **developing** a diagnostic process for rare diseases, and **pilot testing** of critical experimental parameters in a **single** primary care setting

Year 1 → Year 2 → (up to) Year 3

UG3: **$125K** direct costs per year

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

Year 4 → (up to) Year 5

UH3: **$250K** direct costs per year

UG3/UH3 Transition:

- Programmatic 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

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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 provide a description of the hypothesis to be tested in the UH3 phase of the study
  - 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 and 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 2 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 primary care 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. 1)

- 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 primary care setting? To what extent does the application propose sites to be chosen for the UH3 phase representing diverse primary care settings?

Section V: Scored Review Criteria —Specific to this FOA (cont. 2)

- Approach
  - How strong is the justification/rationale that the plan to develop and integrate a machine-learning tool into the diagnostic strategy will result in an improvement in rare disease diagnosis? To what extent will genomic/laboratory panel analyses contribute to an improvement in rare disease diagnosis? How strong is the justification/rationale that the plan to integrate the proposed diagnostic strategy into clinical practice is clear and feasible? To what extent will the measurement tools for assessing healthcare provider uptake and acceptance into clinical care provide interpretable information? For the UH3 phase, how strong is the justification/rationale that the plan for initiating the proposed diagnostic strategy at more than one clinical site is clear and feasible?
  - Milestones: Are appropriate, clearly-defined quantitative milestones provided for the UG3 and UH3 phases of the overall project? Are the UG3 and UH3 milestones feasible, well developed and quantitative with regard to the specific aims within each phase? Is the overall timeline feasible for the UG3 and UH3 phases? Are adequate criteria provided in the UG3 phase to assess milestone completion in order to make a decision to advance studies to the UH3 phase?

Scientific Merit Review

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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 RFA!!!!!!**
   - 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 that 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.

Suggestions!

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 RFA 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.

Frequently Asked Questions

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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 the role of the primary care physician?

- 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 primary care workflow 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 and increase awareness of these patients? They do not have to complete the genomic analysis and interpretation themselves.
- A: 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 primary care physicians.

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 primary care 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 clinicians in more than one setting.
  - Examples include, but are not limited to:
    - Affiliate community sites
    - Satellite primary care clinics
    - Local 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: 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 primary care setting should also be evaluated with quantifiable outcome measures.

Q: What are some key elements to consider in an application for this UG3/UH3 activity code?

- A: The transition plan with clear 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 quantifiable measures of success. A timeline (Gantt chart) including milestones is 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 and will be used to evaluate consideration of the awarded project for funding of non-competing award years.

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 primary care when preparing the application.

Section VII: Agency Contacts

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