Pre-Application Webinar for RFA-TR-20-030: Question & Answer Session

Q1: What is considered a "broad" array of rare diseases?
A1: 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.

The intent of the funding opportunity announcement (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.

Q2: What is the role of the primary care physician?
A2: 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.

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.

Q3: For the UH3 phase, what is considered another clinical setting?
A3: 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

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.

Q4: Given the amount of the award budget, what should be accomplished in the UG3 phase?
A4: The primary focus of the UG3 phase should be on planning and developing a diagnostic process for rare diseases. Pilot testing of critical experimental parameters in a single primary care setting should also be evaluated with quantifiable outcome measures.

Q5: What are some key elements to consider in an application for this UG3/UH3 activity code?
A5: 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.

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.

Q6: What is considered a "multi-disciplinary" team?
A6: 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.

Q7: To be considered responsive, do "front-line" providers need to be primary care providers? For example, could hospital-based providers (i.e., hospitalists or intensive care clinicians) be considered front-line?
A7: 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 providers who see a broad array of patients in the community. It is possible to put together a proposal including hospital-based providers as along as the primary intent of the FOA is met.

Q8: Should the genomic analysis strategy be incorporated in either phase or both?
A8: A strategy for incorporating genomic analysis is required in both phases. The intent of the FOA is to develop a process that would help accelerate the diagnosis of rare diseases patients by considering how the patient would be evaluated. The emphasis here is not specifically on the genomic testing itself.

Q9: Are there instructions regarding font and other formatting rules?
A9: You may review the SF424 (R&R) Application Guide regarding font and other formatting rules. It is critical that applicants follow instructions in the SF424 (R&R) Application Guide except where instructed in this FOA to do otherwise.

Q10: Are the machine learning and genomic sequencing aspects of the FOA required for clinical evaluation by front-line healthcare providers?
A10: The intent of the FOA is to develop a methodology involving front-line healthcare providers, or at some point, helping front-line providers to think about rare diseases and potentially identify a rare disease patient by incorporating this methodology into patient evaluation. There is no requirement that the front-line provider would have to order, complete, or interpret genomic sequencing. For machine learning, an example could include an alert from the electronic health record that could suggest that the front-line provider escalate the patient or notify someone that this is potentially a high-risk patient.

The intent of the FOA is to accelerate moving rare diseases patients along their diagnostic journey. Many patients spend quite a long time before being escalated to expert care centers, and this delay is one area where the diagnostic journey could be shortened. There can be a number of strategies proposed, as long as there is justification as to how this could potentially be successful in shortening the diagnostic odyssey.

Q11: Do we have to select the second site for UH3 for this application or concentrate on the agreement with the primary site?
A11: Within the application, you will need to include a plan for moving to and identifying a second site, as well as moving into the UH3 phase.

Q12: How many awards will be made?
A12: NCATS intends to commit $1,000,000 per year FY2021-2026 to fund up to 4 awards.

Q13: Is there a guide as to what is considered indirect costs?
A13: Clarification of what is considered an indirect cost can be found in the NIH Grants Policy Statement, Section 7.3. Please consult with your office of sponsored programs when creating your budget as they can provide guidance as well.

Q14: Does using purely commercially available genetic testing options count sufficiently towards the genomic analysis component?
A14: It is up to the PI to make the case.

Q15: For the UG3 phase, can the "single primary care setting" include separate pediatric and adult clinics within a single institution?
A15: Yes, it could.

Q16: Do we need to address how to deal with non-coverage of genetic testing from insurance?
A16: No, but the applicant should describe the availability of study components (i.e., genetic testing, machine-learning, and clinical team) and support for the acquisition and administration of these study components.

Q17: Are collaborations with industry as multi-PD/PI or co-investigators appropriate?
A17: Yes, industry can collaborate. Please reference Section III of the FOA for more eligibility information.

Q18: Can an education component be added for the front-line healthcare providers?
A18: It is up to the PI to make the case for an education component.

Q19: Can you elaborate more on the machine learning aspect of the FOA?
A19: The machine learning aspect would be the use of an IT-assist of some kind to help with the acceleration of diagnosis.

- Examples include, but are not limited to:
    - Facial recognition software that may help identify patients with a genetic disorder
    - Augmented reality that would evaluate someone's gait as a potential indicator of a rare disease
    - Develop and apply algorithms to an insurance database to identify patients at high-risk for having a rare disease

Q20: What may be possible models of how patients could or would interact with the research processes? Will the patients know that their data are being studied, and would they have the expectation of being contacted by the project?
A20: Refer to the SF424 (R&R) Application Guide: R.500 – PHS Human Subjects and Clinical Trials Information for instructions regarding informed consent and privacy. When and how to inform patients will depend upon the research plan being proposed by the investigator.

Q21: It seems like activities of this type could fall under the definition of a clinical trial.
A21: 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. Refer to the SF424 (R&R) Application Guide: R.500 – PHS Human Subjects and Clinical Trials Information; 1.4 Clinical Trial Questionnaire. See also the NIH Definition of Clinical Trial Case Studies here: https://grants.nih.gov/policy/clinical-trials/CT-Definition-Case-Studies_1.7.19.pdf.

Q22: Should we submit our current informed consent or IRB materials which already cover human subjects research issues?
A22: Refer to the SF424 (R&R) Application Guide. A human subjects section is required when conducting research on human subjects. Blank informed consent forms are allowed as appendix material.

Q23: Will providing a mechanism to recruit undiagnosed patients for a clinical trial fit the scope of this FOA?
A23: It is up to the PI to make the case.

Q24: Would a proposal focused on diagnosing a small number of esoteric ultra-rare subjects be judged less significant than a larger number of rare (but not ultra-rare) subjects?
A24: No, the prevalence of the rare diseases included in the diagnostic strategy does not impact the proposal's significance. Because most rare diseases are "ultra-rare" or of very low prevalence, accelerating diagnosis in these disorders would be of similar significance to rare diseases of higher prevalence (and vice versa). Please reference Section V of the FOA to see what is scored under the "Significance" review criterion.