

# Part 1. Overview Information

<b>Participating Organization(s)</b>	National Institutes of Health ( <a href="http://www.nih.gov">NIH (http://www.nih.gov)</a> )
<b>Components of Participating Organizations</b>	National Center for Advancing Translational Sciences ( <a href="http://ncats.nih.gov/">NCATS (http://ncats.nih.gov/)</a> ) Eunice Kennedy Shriver National Institute of Child Health and Human Development ( <a href="http://www.nichd.nih.gov/">NICHD (http://www.nichd.nih.gov/)</a> )
<b>Funding Opportunity Title</b>	<b>Clinical Trial Readiness for Rare Diseases, Disorders, and Syndromes (R21 Clinical Trial Not Allowed)</b>
<b>Activity Code</b>	<a href="http://grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r21&amp;Search.x=0&amp;Search.y=0&amp;Search_Type=Activity">R21 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r21&amp;Search.x=0&amp;Search.y=0&amp;Search_Type=Activity)</a> Exploratory/Developmental Research Grant
<b>Announcement Type</b>	New
<b>Related Notices</b>	None
<b>Funding Opportunity Announcement (FOA) Number</b>	<b>PAR-18-953</b>
<b>Companion Funding Opportunity</b>	PAR-18-952, <a href="http://grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r03&amp;Search.x=0&amp;Search.y=0&amp;sort=ac&amp;Search_Type=Activity&amp;text_pre">R03 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r03&amp;Search.x=0&amp;Search.y=0&amp;sort=ac&amp;Search_Type=Activity&amp;text_pre</a> Small Grant Program
<b>Number of Applications</b>	See <a href="#">Section III. 3. Additional Information on Eligibility.</a>
<b>Catalog of Federal Domestic Assistance (CFDA) Number(s)</b>	93.350, 93.865
<b>Funding Opportunity Purpose</b>	This Funding Opportunity Announcement (FOA) invites researchers to submit applications for support of clinical projects that address critical needs for clinical trial readiness in rare diseases. The initiative seeks

applications that are intended to facilitate rare disease research by enabling efficient and effective movement of candidate therapeutics or diagnostics towards clinical trials, and to increase their likelihood of success through development and testing of rigorous biomarkers and clinical outcome assessment measures, or by defining the presentation and course of a rare disease to enable the design of upcoming clinical trials.

## Key Dates

<b>Posted Date</b>	October 4, 2018
<b>Open Date (Earliest Submission Date)</b>	December 07, 2018
<b>Letter of Intent Due Date(s)</b>	30 days prior to receipt date
<b>Application Due Date(s)</b>	January 7, 2019, June 10, 2019, October 24, 2019, June 8, 2020, October 26, 2020, June 7, 2021, October 25, 2021, by 5:00 PM local time of applicant organization. All <a href="#">types of non-AIDS applications</a> allowed for this funding opportunity announcement are due on these dates. Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.
<b>AIDS Application Due Date(s)</b>	Not Applicable.
<b>Scientific Merit Review</b>	April 2019, October 2019, February 2020, October 2020, February 2021, October 2021, February 2022
<b>Advisory Council Review</b>	May 2019, January 2020, May 2020, January 2021, May 2021, January 2022, May 2022
<b>Earliest Start Date</b>	July 2019, April 2020, July 2020, April 2021, July 2021, April 2022, July 2022
<b>Expiration Date</b>	October 26, 2021
<b>Due Dates for E.O. 12372</b>	Not Applicable

### Required Application Instructions

It is critical that applicants follow the instructions in the Research (R) Instructions in the [SF424 \(R&R\) Application Guide \(\[url\\\_redirect.htm?id=12000\]\(https://grants.nih.gov/grants/guide/url\_redirect.htm?id=12000\)\)](#), except where instructed to do otherwise (in this

FOA or in a Notice from [NIH Guide for Grants and Contracts \(//grants.nih.gov/grants/guide/\)](http://grants.nih.gov/grants/guide/).

Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in [Section IV](#). When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions.

**Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options available to submit your application through Grants.gov to NIH and Department of Health and Human Services partners. You **must** use one of these submission options to access the application forms for this opportunity.

1. Use the NIH ASSIST system to prepare, submit and track your application online.

[Apply Online Using ASSIST](#)

2. Use an institutional system-to-system (S2S) solution to prepare and submit your application to Grants.gov and [eRA Commons \(http://public.era.nih.gov/commons/\)](http://public.era.nih.gov/commons/) to track your application. Check with your institutional officials regarding availability.
3. Use [Grants.gov \(http://www.grants.gov/web/grants/applicants/download-application-package.html#search=true&oppNum=PAR-18-953\)](http://www.grants.gov/web/grants/applicants/download-application-package.html#search=true&oppNum=PAR-18-953) Workspace to prepare and submit your application and [eRA Commons \(http://public.era.nih.gov/commons/\)](http://public.era.nih.gov/commons/) to track your application.

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## Part 2. Full Text of Announcement

### Section I. Funding Opportunity Description

#### **Purpose**

Attaining effective therapies for rare diseases is challenging due to their low prevalence resulting in fewer patients, clinicians, researchers, and resources compared to common diseases. This leads to gaps in our understanding of a rare disease's natural history, and a dearth of suitable biomarkers or clinical outcome measures, or of other components needed to design, conduct, and interpret rigorous clinical trials.

This Funding Opportunity Announcement (FOA) invites researchers to submit applications for support of clinical projects that address critical needs for clinical trial readiness in rare diseases. The Office of Rare Diseases Research (ORDR) within the National Center for Advancing Translational Sciences (NCATS) along with the Institutes and Centers (ICs) listed in Part I at the National Institutes of Health (NIH) intend to facilitate rare disease research by enabling efficient and effective movement of candidate therapeutics or diagnostics towards clinical trials, and to increase their likelihood of success through development and testing of rigorous biomarkers and clinical outcome assessment measures, or by defining the presentation and course of a rare disease to enable the design of upcoming clinical trials.

### **Background**

The NIH supports translational and clinical research on a broad range of diseases that are defined as rare; that is, diseases affecting fewer than 200,000 individuals in the United States (per the [Rare Diseases Act of 2002](https://history.nih.gov/research/downloads/PL107-280.pdf) (<https://history.nih.gov/research/downloads/PL107-280.pdf>)). Collectively, there are an estimated 7,000 rare diseases, which affect approximately 25-30 million people in the United States. Most are serious or life-threatening, leading to significant morbidity and mortality, and most affect children. Despite advances in our understanding of the causes and mechanisms of many rare diseases, effective treatments are available for fewer than 5%. To address this significant public health concern, the NIH investment into discovery research has contributed to unprecedented opportunities to translate scientific advances into better treatments. Gene therapy and related approaches are an example of opportunities that have resulted from technological advances. However, to evaluate such potentially transformative treatments, researchers, biopharmaceutical companies, and regulators need high quality, natural history data, as well as biological and clinical outcome measures fit for the intended purpose. The absence of such information often represents a bottleneck in therapy development for many rare diseases. This initiative aims to support studies that address these gaps in understanding of disease natural history and appropriate outcome measures. Given the large number of rare diseases and the limited funding available, this initiative will focus on studies for which it can be demonstrated that there are clinical development candidates for the indication, and for which there are unmet medical needs. The initiative will promote partnerships among academic investigators, industry, and patient groups, and will encourage interactions with the Food and Drug Administration (FDA). Use of existing data standards, tools, information technology platforms, and candidate clinical outcomes measures and biomarkers will also be encouraged, rather than the discovery or de novo development of such tools and resources.

### **Definitions**

This FOA describes a specialized type of clinical research that is intended to provide data necessary for the design of future clinical trials.

Clinical trial readiness is the state of having validated clinical research tools and knowledge of disease natural history necessary for the design of efficient clinical trials. Validated clinical research tools can include biomarkers or clinical outcome assessment measures that are fit-for-purpose within a defined context of use relevant to the clinical trials. Knowledge of disease natural history necessary for clinical trial design can include characteristics for stratification or determining inclusion and exclusion criteria; the stage of disease progression that may be responsive to treatment; and data needed for determining sample size through power calculations.

This FOA uses terminology defined in the [BEST \(Biomarkers, EndpointS, and Other Tools\) Resource](https://www.ncbi.nlm.nih.gov/books/NBK326791/) (<https://www.ncbi.nlm.nih.gov/books/NBK326791/>), which was developed by the FDA-NIH Biomarker Working Group. Investigators are encouraged to use the terms below, where appropriate in their applications. Guidance to reviewers will include these definitions as a way to promote consistent evaluation of the applications. (See <https://www.ncbi.nlm.nih.gov/books/NBK338448/> (<https://www.ncbi.nlm.nih.gov/books/NBK338448/>) for reference to the BEST Resource's glossary for the following definitions.)

**Biomarker** – A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic,

radiographic, or physiologic characteristics are types of biomarkers. Categories of biomarkers include: Susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, safety. Clinical outcome assessment (COA) – An assessment of an outcome that reflects how an individual feels, functions or survives. The four types of COAs are clinician-reported, observer-reported, patient-reported, and performance outcomes.

Context of Use (COU) – A statement that fully and clearly describes the way the [medical product development tool](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/medical-product-development-tool/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/medical-product-development-tool/>) is to be used and the medical product development-related purpose of the use.

Concept – In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the [assessment](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/assessment/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/assessment/>) is intended to capture (or reflect).

Validation – A process to establish that the performance of a [test, tool, or instrument](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/test-tool-or-instrument/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/test-tool-or-instrument/>) is acceptable for its intended purpose. For this FOA, the intended purpose should be the collection of data in a clinical trial that will be used to determine whether to move forward with the intervention being tested to a later stage trial or for regulatory approval. Applications to this FOA should focus on clinical validation. Biochemical and molecular biomarkers should have substantial data supporting analytical validation collected prior to submission of an application to this FOA.

- *Analytical Validation* – A process to establish that the performance characteristics of a [test, tool, or instrument](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/test-tool-or-instrument/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/test-tool-or-instrument/>) are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.
- *Clinical Validation* – A process to establish that the [test, tool, or instrument](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/test-tool-or-instrument/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/test-tool-or-instrument/>) acceptably identifies, measures or predicts the [concept](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/concept/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/concept/>) of interest.
- *Construct Validity* – A process to establish, using quantitative methods, the extent to which the relationships among items, domains, and concepts of a clinical outcome assessment conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.
- *Content Validity* – A process to establish from qualitative research the extent to which the clinical outcome assessment instrument measures the [concept](https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/concept/) (<https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/concept/>) of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use.

## Scope

To optimize clinical trial readiness, there needs to be sufficient understanding of the rare disease to permit design, conduct, and interpretation of rigorous clinical trials. FDA published [Draft Guidance](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf) (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf>) on common issues in drug development for rare diseases. This FOA is intended to support studies that address some of the issues presented in this guidance document, including the need for adequate understanding of the course of the disease and the need for sensitive and reliable biomarkers and outcome measures to be used during a clinical trial.

The proposed studies should have a research question able to be addressed within the defined timeline. The projects should not include clinical trials. If considering clinical trials, then please reference the NCATS website for other [open opportunities](https://ncats.nih.gov/funding/open) (<https://ncats.nih.gov/funding/open>).

Applicants are expected to have clinical expertise for the rare disease under study, including the capability for measuring COAs and analyzing appropriate biomarkers where applicable. Applicants should also have sufficient numbers of rare disease patients for inclusion in the study or have access to additional patients through collaboration.

Projects appropriate for this initiative need not be high risk/high reward studies; however, they should advance the field by facilitating clinical trial readiness through the development of missing components that are essential for rigorous clinical trials. Projects should be distinct from those supported through the traditional R01 mechanism and should have a broader scope than those suited for an R03.

Projects that are appropriate for this FOA should focus on diseases that lack critical components of trial readiness and should have candidate therapeutics that will be ready for testing in clinical trials by the time the trial readiness study is completed. For the purpose of this initiative, clinical trial readiness can include two categories of projects:

- 1) Those that define the presentation and course of the rare disease (e.g., natural history studies including retrospective projects, and longitudinal or cross-sectional approaches), in ways that are essential for the design of upcoming clinical trials.
- 2) Those that utilize sensitive, reliable, valid, and responsive tools to identify or select appropriate participants for clinical trials, or to measure the effects of interventions. These tools include COA measures and biomarkers. Investigators are encouraged to use or modify existing resources, validate existing tools in specific rare disease populations, or add components to existing disease-specific tools (such as symptom scales).

This FOA will support applications for testing of biomarkers or outcome measures so that they are ready for use in multi-site studies. Biochemical or molecular biomarkers should include justification that describes accuracy, precision, analytical sensitivity, analytical specificity including interfering substances, dynamic range, and expected normal values. For imaging, radiological, or physiological biomarkers, the justification should provide preliminary data on the accuracy, reproducibility, sensitivity, and specificity as determined by study of a patient cohort (but not necessarily in the same rare disease). An appropriate study could start with a small manageable set of candidate biomarkers, and based on data acquired during the study, be narrowed down to one or a few appropriate biomarkers for use in a clinical trial.

Examples of studies intended to be supported through this FOA include, but are not limited to, the following:

- Studies aimed at the clinical validation of biomarkers or COAs with defined contexts of use in specific rare disease populations.
- Proof of concept studies in an animal model of a rare disease.
- Studies to develop or incorporate patient-reported or patient-centered outcomes.
- Studies to characterize rare disease patient cohorts regarding COA measures, biomarkers, genetic, epigenetic, or physiological factors that will be used to stratify patients or determine inclusion/exclusion criteria in upcoming clinical trials.
- Studies to characterize rare disease patient cohorts using candidate outcome measures to establish the variability of measures as needed for accurate power calculations or to determine the appropriate duration of upcoming clinical trials.
- Studies evaluating the responsiveness of biomarkers or COAs through the observation of patients who are receiving treatment as part of their clinical care.
- Studies to address knowledge gaps for clinical trial planning that also pilot innovative recruitment strategies for women, minorities, and other underserved populations who would be candidates for participation in upcoming rare disease trials.
- Studies that modify use of a tool in a specific rare disease population, such as the addition of disease-specific modules to an existing tool (e.g., disease-specific symptom scales).
- Ancillary studies that leverage ongoing clinical studies supported through other sources of funding.

Examples of studies that are considered not appropriate for this FOA include, but are not limited to, the following:

- Natural history studies aimed at broadly exploring disease pathophysiology, genetic or epigenetic mechanisms with no direct connection to an upcoming clinical trial are outside the scope of this FOA. Studies of patient genetics or pathophysiology would be in scope only if characterization is necessary for stratifying trial participants or determining inclusion/exclusion criteria in upcoming clinical trials.
- Studies of biomarker discovery should seek funding through the parent FOAs for research project grants.
  - To be considered for support through this FOA, the biochemical or molecular biomarker analytical assay(s) should be already characterized in terms of accuracy, precision, analytical sensitivity and specificity, effects of interfering substances, dynamic range, and expected normal values. It is not the intent of this FOA to support studies of biomarker discovery or assay characterization.
- Applications that propose only to maintain patient registries will not be considered for funding. NCATS and the ICs listed in Part I at NIH do not intend to provide support to maintain or acquire additional data on study participants beyond the end of the clinical trial readiness grant.
- Applications that request support for infrastructure to establish new clinical trial networks are beyond the scope of this FOA. Applicants should leverage existing resources such as existing rare disease-focused networks (such as the [RDCRN \(https://www.rarediseasesnetwork.org/\)](https://www.rarediseasesnetwork.org/)).

No studies aimed at determining the safety, pharmacokinetics, efficacy, or effectiveness of an intervention (drug, biologic, device, etc.) will be supported through this mechanism.

### **Leveraging Existing Research Resources**

Applicants should leverage existing research resources for their clinical trial readiness studies. Such resources may include existing clinical research networks such as [RDCRN \(https://www.rarediseasesnetwork.org/\)](https://www.rarediseasesnetwork.org/), [NeuroNEXT \(https://www.neuronext.org/\)](https://www.neuronext.org/), or other existing networks that have successfully conducted studies of rare diseases. Also, applicants should leverage existing research resources to streamline multi-center studies, such as the [SMART IRB \(https://smartirb.org/\)](https://smartirb.org/). Leveraging the resources and support from advocacy groups, private research foundations, academic institutions, other government agencies, and the NIH Intramural program are also encouraged. Researchers interested in conducting trial readiness studies through RDCRN should contact the NCATS Scientific/Research Contact listed in the [Agency Contacts](#) section below early in the process of designing the study.

Studies that leverage the resources of ongoing clinical trials or longitudinal studies supported through other Federal or private funds are also encouraged. Researchers may consider collecting data to characterize new or improved COA measures, biomarkers, or approaches as ancillary studies to ongoing clinical trials or longitudinal studies. Investigators are encouraged to collect the clinical data needed to apply to the FDA for qualification of biomarkers or COAs intended to be used in the regulatory review process. Researchers are encouraged to seek advice from the FDA on the development of the COA or biomarker. The FDA provides additional information about the Drug Development Tools Qualification Programs on its website.

Participating NIH Institutes and Centers are unlikely to support more than one clinical trial readiness study in any one disease. Investigators are encouraged to coordinate efforts among researchers with common interests to develop a study that is both necessary and sufficient for achieving trial readiness.

See [Section VIII. Other Information](#) for award authorities and regulations.

## **Section II. Award Information**

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### **Funding Instrument**

Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.

<b>Application Types Allowed</b>	<p>New Resubmission</p> <p>The <a href="https://grants.nih.gov/grants/guide/url_redirect.htm?id=11116">OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116)</a> and the SF424 (R&amp;R) Application Guide provide details on these application types.</p>
<b>Clinical Trial?</b>	<p>Not Allowed: Only accepting applications that do not propose clinical trials <a href="https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370">Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)</a></p>
<b>Funds Available and Anticipated Number of Awards</b>	<p>The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.</p>
<b>Award Budget</b>	<p>Applications can request budgets that are up to \$275,000 direct costs for the 2-year project period of the award. No more than \$200,000 direct costs may be requested in any single year.</p>
<b>Award Project Period</b>	<p>Applications may request no more than 2 years.</p>

NIH grants policies as described in the [NIH Grants Policy Statement \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11120\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11120) will apply to the applications submitted and awards made from this FOA.

## Section III. Eligibility Information

### 1. Eligible Applicants

#### Eligible Organizations

##### Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

##### Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)



## For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

## Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government - Including NIH Intramural Program
- U.S. Territory or Possession

## Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations

## Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are not** eligible to apply

Non-domestic (non-U.S.) components of U.S. Organizations **are not** eligible to apply.

Foreign components, as [defined in the NIH Grants Policy Statement \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11118\)](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11118), **are** allowed.

## Required Registrations

### Applicant organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The [NIH Policy on Late Submission of Grant Applications \(//grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html\)](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html) states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- [Dun and Bradstreet Universal Numbering System \(DUNS\) \(http://fedgov.dnb.com/webform\)](http://fedgov.dnb.com/webform) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- [System for Award Management \(SAM\) \(https://www.sam.gov/portal/public/SAM/\)](https://www.sam.gov/portal/public/SAM/) (formerly CCR) – Applicants must complete and maintain an active registration, which requires renewal at least annually. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.

- [NATO Commercial and Government Entity \(NCAGE\) Code](https://grants.nih.gov/grants/guide/redirect.htm?id=11176) ([//grants.nih.gov/grants/guide/redirect.htm?id=11176](https://grants.nih.gov/grants/guide/redirect.htm?id=11176)) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- [eRA Commons](https://grants.nih.gov/grants/guide/redirect.htm?id=11123) ([//grants.nih.gov/grants/guide/redirect.htm?id=11123](https://grants.nih.gov/grants/guide/redirect.htm?id=11123)) - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

### **Program Directors/Principal Investigators (PD(s)/PI(s))**

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

### **Eligible Individuals (Program Director/Principal Investigator)**

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

## **2. Cost Sharing**

This FOA does not require cost sharing as defined in the [NIH Grants Policy Statement](https://grants.nih.gov/grants/guide/redirect.htm?id=11126). ([//grants.nih.gov/grants/guide/redirect.htm?id=11126](https://grants.nih.gov/grants/guide/redirect.htm?id=11126))

## **3. Additional Information on Eligibility**

### **Number of Applications**

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see [NOT-OD-11-101](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html) ([//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html)))

## **Section IV. Application and Submission Information**

### **1. Requesting an Application Package**

Buttons to access the online ASSIST system or to download application forms are available in [Part 1](#) of this FOA. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

## 2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the Research (R) Instructions in the [SF424 \(R&R\) Application Guide \(\[http://grants.nih.gov/grants/guide/url\\\_redirect.htm?id=12000\]\(http://grants.nih.gov/grants/guide/url\_redirect.htm?id=12000\)\)](#) except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review. For information on Application Submission and Receipt, visit [Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications \(\[http://grants.nih.gov/grants/guide/url\\\_redirect.htm?id=41137\]\(http://grants.nih.gov/grants/guide/url\_redirect.htm?id=41137\)\)](#).

### Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

By the date listed in [Part 1. Overview Information](#), prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity

The letter of intent should be sent to:

Carol Lambert, Ph.D.

Telephone: 301-435-0814

Fax: 301-480-3660

Email: [lambert@mail.nih.gov](mailto:lambert@mail.nih.gov) (<mailto:xxxx@mail.nih.gov>)

### Page Limitations

All page limitations described in the SF424 Application Guide and the [Table of Page Limits \(\[http://grants.nih.gov/grants/guide/url\\\_redirect.htm?id=11133\]\(http://grants.nih.gov/grants/guide/url\_redirect.htm?id=11133\)\)](#) must be followed

### Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

#### **SF424(R&R) Cover**

All instructions in the SF424 (R&R) Application Guide must be followed.

#### **SF424(R&R) Project/Performance Site Locations**

All instructions in the SF424 (R&R) Application Guide must be followed.

#### **SF424(R&R) Other Project Information**

All instructions in the SF424 (R&R) Application Guide must be followed.

#### **SF424(R&R) Senior/Key Person Profile**

All instructions in the SF424 (R&R) Application Guide must be followed.

#### **R&R or Modular Budget**

All instructions in the SF424 (R&R) Application Guide must be followed.

## R&R Subaward Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

## PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

## PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

### Research Strategy:

**Evidence Supporting Rare Disease Classification** - The Significance section of the Research Strategy should include a paragraph with the heading "*Evidence Supporting Rare Disease Classification*". This section should provide the evidence that the disease/condition being studied is classified as a rare disease; i.e. that there are 200,000 or fewer patients in the U.S. This section may include one or more references confirming the prevalence of the disease/condition that is the primary focus of the research application. If the disease/condition has been granted orphan status by the FDA, provide this information in this paragraph. If it is a rare variant or subset of a more common condition, provide the rationale for focusing a trial readiness study on this variant. Describe the scientific basis for separating biomarker/COA validation for this rare variant or subset from that of the common condition.

**Need for Clinical Trial Readiness** - The Significance section of the Research Strategy should also include a subsection with the heading "*Urgent Need for Clinical Trial Readiness*". This subsection should describe the need for conducting the trial readiness study at this time. Applicants should describe the clinical trial design issues (e.g., biomarker or COA validation or qualification, data for power calculations, defining inclusion/exclusion criteria, determining the duration of the trial, etc.) that will be addressed by this trial readiness study. Describe the potential impact of the proposed studies in addressing significant needs in the design and increasing the likelihood of success of upcoming clinical trials.

This section should also contain the following:

- A brief description of the state of development of candidate therapeutics or devices for this rare disease (even if the current applicants are not involved in the development of those therapeutics/devices).
- Timelines for the advance of therapeutics/devices to clinical trials.
- A brief description of the clinical trial(s) that would be enabled by the results of this trial readiness study.
- Include a brief description of the currently available COA measures and/or biomarkers. If appropriate for the proposed study, describe how the study will result in advancements over the currently available measures/biomarkers. If the current measures/biomarkers are considered inadequate or insufficiently developed for use in upcoming trials, describe their limitations and how those limitations may compromise the success of upcoming trials. If the proposed trial readiness study is ancillary to an ongoing clinical trial or longitudinal study, describe that study and provide a letter of support (below) from the study's lead PD(s)/PI(s). Explain how the trial readiness study will lead to improvements in the design of future trials above that of the ongoing study.
- Describe any gaps in knowledge regarding the disease natural history that need to be addressed to achieve clinical trial readiness. Explain how the lack of this knowledge will compromise clinical trial design and how this study will overcome current obstacle(s).
- Briefly describe the role of companies or voluntary health organizations that is currently in place or potentially available for clinical trial readiness studies or clinical trials for this disease, if applicable.

## Biomarkers and Their Context of Use

If biomarker validation is proposed, the approach section of the application should contain a subsection with the heading “ *Biomarkers and Their Context of Use*”. This section could describe each biomarker that will be tested for validation and the context of use (COU). The COU should explain how, when and why the biomarker is to be used in a clinical trial.

Biochemical/molecular biomarkers must have analytical validation before applying for a clinical trial readiness award through this program. Applications should include a table listing each biochemical/molecular biomarker to be tested for clinical validation, the intended use (e.g., diagnostic, predictive, treatment response, pharmacodynamic), the method of the assay (e.g., mass spectrometry, ELISA, surface plasmon resonance), the sensitivity, dynamic range and expected normal values. Other characteristics of the assay such as specificity, precision, interfering substances, etc. should also be described in the text of this subsection. Describe what a graph of each biomarker measurement over time is expected to show (e.g., linearly decreasing measurement, sigmoidal curve, etc.) and the expected relationship of the biomarker to COA measures (e.g., inversely proportional).

For imaging, radiological, or physiological biomarkers, the rationale should provide preliminary data on the accuracy, reproducibility, sensitivity, and specificity as determined by study of a patient cohort (but not necessarily in the same disease). Describe the equipment (i.e., instrument manufacturer and model) and expertise available at each clinical site for measuring the biomarker(s). Plans for the training of personnel at each site in the use of the standardized protocols, data quality control strategies, reference standards and approaches for verifying instrument calibration at the clinical sites should also be described as appropriate.

### **Clinical Outcome Assessment Measures**

Clinical outcome assessment (COA) measures can be clinician-, observer-, or patient-reported, or a performance outcome. If COA measure validation is proposed, provide a list of each COA measure that the study aims to clinically validate. Describe the construct validity (i.e., hypothesized relationship with other disease characteristics) and content validity (i.e., extent to which the COA measures the concept of interest) for each COA measure (also see Definitions section above). Describe plans for analysis of test-retest and inter-rater reliability. Describe Rasch analysis for COA measure optimization if appropriate.

### **Natural History Studies**

Studies of the natural history of the disease may only be proposed for the purpose of developing readiness for upcoming clinical trials. If a natural history study is proposed, provide a rationale for how the natural history study will support advancement of the development of a rare disease medical product through characterization of an aspect of the disease natural history that must be addressed before a clinical trial can be planned or initiated (such as characterization of an external control group, identification of genotypic or phenotypic subpopulations necessary for defining inclusion/exclusion criteria, or other components of study design), and that the natural history study can address this characterization within the study timeframe.

### **Statistical Analysis Plans**

Include a section describing the plans for statistical analysis of the data and tests for validation of biomarkers/COA or analysis of the natural history study results. Explain the decision for selecting the statistical analysis methods— what methods were considered; why were the proposed methods chosen. Describe sample size considerations for

the biomarkers and COAs, or disease natural history characterization proposed. Statistical analysis of convergent validity of COA measures and biomarkers is often an important component of trial readiness studies. Describe which biomarkers and COA measures will be tested for convergent validity if appropriate for the study.

### **Existing Clinical Networks**

For ancillary studies, briefly describe the aims of the parent study and the timeline of the parent study relative to the proposed ancillary study. The application should discuss the additional burden to the participants of the parent study and whether consent obtained from the participants is adequate to cover the ancillary study or if additional consent must be obtained. (See also Letters of Support)

### **Letters of Support**

Provide letters of collaboration from individuals who will contribute in a substantive, meaningful way to the scientific development or execution of the project, whether or not salaries are requested. As appropriate, letters should document access to expertise, equipment and/or patients.

For ancillary studies, provide a letter of support from the PD/PI of the parent study that includes:

- A brief description of the aims of the parent study
- The timeline of the parent study relative to the proposed ancillary study

**Resource Sharing Plan:** Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide.

The following modifications also apply:

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan.
- The Resource Sharing Plan should include a timeline for publications and access to additional study data and biospecimens, where applicable. It should describe the process for evaluating requests for access to the data and/or biospecimens, and the expected time from when the request is received to when the sharing of data/biospecimens is achieved.

### **Appendix:**

Only limited Appendix materials are allowed. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

The Appendix must include the following, as appropriate for the proposed study:

- Standardized protocols for measuring the biomarkers or evaluating the COA proposed
- For proposed ancillary studies, provide the protocol for the parent clinical trial or longitudinal study and the consent form for the parent study
- Meeting minutes or advice letters provided by the FDA regarding qualification or discussions from Critical Path Innovation Meetings (CPIM) or other early interaction meetings of the proposed biomarker(s), COA measure(s), or natural history studies
- Although the expanded access regulatory pathway would not typically be used for this FOA, where applicable, protocols used for expanded access studies or documentation submitted to FDA to initiate and amend expanded access protocols must be included in the appendix

### **PHS Human Subjects and Clinical Trials Information**

When involving NIH-defined human subjects research, clinical research, and/or clinical trials (and when applicable,

clinical trials research experience) follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered “Yes” to the question “Are Human Subjects Involved?” on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or **Delayed Onset Study** record.

#### **Study Record: PHS Human Subjects and Clinical Trials Information**

All instructions in the SF424 (R&R) Application Guide must be followed.

#### **Delayed Onset Study**

All instructions in the SF424 (R&R) Application Guide must be followed.

#### **PHS Assignment Request Form**

All instructions in the SF424 (R&R) Application Guide must be followed.

### **3. Unique Entity Identifier and System for Award Management (SAM)**

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov

### **4. Submission Dates and Times**

[Part I. Overview Information](#) contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or [Federal holiday](#) ([https://grants.nih.gov/grants/guide/url\\_redirect.html?id=82380](https://grants.nih.gov/grants/guide/url_redirect.html?id=82380)), the application deadline is automatically extended to the next business day.

Organizations must submit applications to [Grants.gov](#) ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11128](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11128)) (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the [eRA Commons](#) ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11123](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11123)), NIH’s electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Applications that miss the due date and time are subjected to the NIH Policy on Late Application Submission.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

### **5. Intergovernmental Review (E.O. 12372)**

This initiative is not subject to [intergovernmental review](#). ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11142](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11142))

### **6. Funding Restrictions**

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the [NIH Grants Policy Statement](#) ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11120](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11120)).

Pre-award costs are allowable only as described in the [NIH Grants Policy Statement \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11143\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11143).

## 7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted.

Applicants must complete all required registrations before the application due date. [Section III. Eligibility Information](#) contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit [Applying Electronically \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11144\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11144). If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the [Guidelines for Applicants Experiencing System Issues \(//grants.nih.gov/grants/ElectronicReceipt/support.htm#guidelines\)](https://grants.nih.gov/grants/ElectronicReceipt/support.htm#guidelines). For assistance with application submission, contact the Application Submission Contacts in [Section VII](#).

### Important reminders:

All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package. Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH. See [Section III](#) of this FOA for information on registration requirements.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.

See [more tips \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11146\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11146) for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review, NIH. Applications that are incomplete or non-compliant will not be reviewed.

### Applications Involving the NIH Intramural Research Program

The requests by NIH intramural scientists will be limited to the incremental costs required for participation. As such, these requests will not include any salary and related fringe benefits for career, career conditional or other Federal employees (civilian or uniformed service) with permanent appointments under existing position ceilings or any costs related to administrative or facilities support (equivalent to Facilities and Administrative or F&A costs). These costs may include salary for staff to be specifically hired under a temporary appointment for the project, consultant costs, equipment, supplies, travel, and other items typically listed under Other Expenses. Applicants should indicate the number of person-months devoted to the project, even if no funds are requested for salary and fringe benefits. If selected, appropriate funding will be provided by the NIH Intramural Program. NIH intramural scientists will participate in this program as PDs/PIs in accord with the Terms and Conditions provided in this FOA. Intellectual property will be managed in accord with established policy of the NIH in compliance with Executive Order 10096, as amended, 45 CFR Part 7; patent rights for inventions developed in NIH facilities are NIH property unless NIH waives its rights.

Should an extramural application include the collaboration with an intramural scientist, no funds for the support of the intramural scientist may be requested in the application. The intramural scientist may submit a separate request for intramural funding as described above.

### Use of Common Data Elements in NIH-funded Research



Many NIH ICs encourage the use of common data elements (CDEs) in basic, clinical, and applied research, patient registries, and other human subject research to facilitate broader and more effective use of data and advance research across studies. CDEs are data elements that have been identified and defined for use in multiple data sets across different studies. Use of CDEs can facilitate data sharing and standardization to improve data quality and enable data integration from multiple studies and sources, including electronic health records. NIH ICs have identified CDEs for many clinical domains (e.g., neurological disease), types of studies (e.g. genome-wide association studies (GWAS)), types of outcomes (e.g., patient-reported outcomes), and patient registries (e.g., the Global Rare Diseases Patient Registry and Data Repository). NIH has established a "Common Data Element (CDE) Resource Portal" (<http://cde.nih.gov/>) to assist investigators in identifying NIH-supported CDEs when developing protocols, case report forms, and other instruments for data collection. The Portal provides guidance about and access to NIH-supported CDE initiatives and other tools and resources for the appropriate use of CDEs and data standards in NIH-funded research. Investigators are encouraged to consult the Portal and describe in their applications any use they will make of NIH-supported CDEs in their projects.

### **Prior Consultation with Scientific/Research Staff**

Applicants are encouraged to consult with NIH Scientific/Research Staff early on during the planning for an application. This early contact will provide an opportunity to discuss and clarify NIH policies and guidelines, including the scope of project relative to the NIH mission and intent of this FOA. These discussions also provide important information and guidance on how to develop an appropriate timeline and milestone plan, which are subject to peer review under this program.

### **Post Submission Materials**

Applicants are required to follow the instructions for post-submission materials, as described in [the policy](http://grants.nih.gov/grants/guide/uri_redirect.htm?id=82299) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=82299](http://grants.nih.gov/grants/guide/uri_redirect.htm?id=82299)). Any instructions provided here are in addition to the instructions in the policy.

## **Section V. Application Review Information**

### **1. Criteria**

Only the review criteria described below will be considered in the review process. As part of the [NIH mission](http://grants.nih.gov/grants/guide/uri_redirect.htm?id=11149) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11149](http://grants.nih.gov/grants/guide/uri_redirect.htm?id=11149)), all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

For this particular announcement, note the following:

The R21 exploratory/developmental grant supports investigation of novel scientific ideas or new model systems, tools, or technologies that have the potential for significant impact on biomedical or biobehavioral research. An R21 grant application need not have extensive background material or preliminary information. Accordingly, reviewers will emphasize the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. Preliminary data are not required for R21 applications; however, they may be included if available.

### **Overall Impact**

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

### **Scored Review Criteria**

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate

score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

### **Significance**

Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

**Specific to this FOA:** How strong is the rationale in the application that the disease or condition meets the criteria of being rare (fewer than 200,000 patients in the U.S., and/or documentation of FDA orphan status)? Projects appropriate for this initiative need not be high risk/high reward studies; however, they should advance the field by facilitating clinical trial readiness through the development of missing components that are essential for rigorous clinical trials. How is this project moving the field forward and making a difference for clinical trials?

If the application is for a rare variant or subset of a more common condition, how strong is the rationale that a separate clinical trial readiness activity should focus on this rare form?

How does the project address a significant, unmet need for clinical trial readiness, or a critical barrier or bottleneck to progress toward clinical trials? How does this application address a gap in understanding of disease natural history that would meaningfully improve knowledge needed to design and implement a clinical trial of a candidate therapeutic; or achieve outcome measure and/or biomarker clinical validation? How likely are the proposed studies to establish clinically validated biomarkers and/or COA measures with well-defined contexts of use, or to fill gaps in understanding the disease natural history that are currently obstacles for the design of upcoming clinical trials?

As appropriate, how clearly does the application describe the COU of the biomarker or outcome measure such that it will enable the design of upcoming clinical trials?

How will the readiness study increase the likelihood of success of upcoming trials?

How does this proposed study relate to other ongoing efforts for this rare disease? Consider whether there is overlap with ongoing efforts or missed opportunities for coordinated efforts in the same rare disease.

How strong is the rationale that there is urgency and that there will be candidate therapeutics ready for testing in clinical trials at the time of completion of the proposed trial readiness study?

For studies that are ancillary to an ongoing clinical trial or longitudinal study, how will it advance the design of future trials beyond that of the parent study? How will the additional burden of the ancillary study affect the participants in the parent study? How well does the consent obtained for participation in the parent study relate to consent for the ancillary study?

### **Investigator(s)**

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

### **Innovation**

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the

concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

### **Approach**

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

**Specific to this FOA:** How well does the application describe plans to ensure that the study is scientifically rigorous, controls are in place to minimize bias, and reporting is transparent?

How well characterized are the assays for biochemical or molecular biomarkers in terms of accuracy, precision, sensitivity, selectivity, dynamic range, and expected normal values?

How well optimized and ready for implementation in a multi-site study are the methods for measuring imaging, radiological or physiological biomarkers, and/or COAs?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

### **Environment**

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

**Specific to this FOA:** Do the clinical sites provide access to a sufficient number of patients with the rare disease to support enrollment for the study?

How strong is the justification that all of the participating clinical sites have the appropriate expertise and equipment for measuring COAs and analyzing appropriate biomarkers?

### **Additional Review Criteria**

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

#### **Protections for Human Subjects**

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of

research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the [Guidelines for the Review of Human Subjects \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11175\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

### **Inclusion of Women, Minorities, and Children**

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the [Guidelines for the Review of Inclusion in Clinical Research \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11174\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

### **Vertebrate Animals**

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the [Worksheet for Review of the Vertebrate Animal Section \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11150\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

### **Biohazards**

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

### **Resubmissions**

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

### **Renewals**

Not applicable.

### **Revisions**

Not applicable.

### **Additional Review Considerations**

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

#### **Applications from Foreign Organizations**

Not applicable.

## Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

## Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: (1) [Data Sharing Plan](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11151) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11151](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11151)); (2) [Sharing Model Organisms](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11152) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11152](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11152)); and (3) [Genomic Data Sharing Plan \(GDS\)](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11153) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11153](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11153)).

## Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

## Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

## 2. 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](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11154) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11154](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11154)), using the stated [review criteria](#). Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- Will receive a written critique.

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications.. Following initial peer review, recommended applications will receive a second level of review by the NCATS Advisory Council or the councils of the other Institutes or Centers participating in this FOA. 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.

## 3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the [eRA Commons](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11123) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11123](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11123)). Refer to Part 1 for dates for peer review, advisory council review, and earliest start date.

Information regarding the disposition of applications is available in the [NIH Grants Policy Statement](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11156) ([//grants.nih.gov/grants/guide/uri\\_redirect.htm?id=11156](https://grants.nih.gov/grants/guide/uri_redirect.htm?id=11156)).

## Section VI. Award Administration Information

### 1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the [NIH Grants Policy Statement \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11157\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11157).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in [Section IV.5. Funding Restrictions](#). Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to terms and conditions found on the [Award Conditions and Information for NIH Grants \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11158\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11158) website. This includes any recent legislation and policy applicable to awards that is highlighted on this website.

### 2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the [NIH Grants Policy Statement \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11120\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11120) as part of the NoA. For these terms of award, see the [NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11157\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11157) and [Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11159\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11159). More information is provided at [Award Conditions and Information for NIH Grants \(//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11158\)](https://grants.nih.gov/grants/guide/url_redirect.htm?id=11158).

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), NIH awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIS) requirements. FAPIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIS, in making a judgement about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 "Federal awarding agency review of risk posed by applicants." This provision will apply to all NIH grants and cooperative agreements except fellowships.

For additional guidance regarding how the provisions apply to NIH grant programs, please contact the

Scientific/Research Contact that is identified in Section VII under Agency Contacts of this FOA. HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English proficiency. Please see <http://www.hhs.gov/ocr/civilrights/resources/laws/revisedlep.html>. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see <http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html> (<http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html>); and <http://www.hhs.gov/ocr/civilrights/understanding/index.html> (<http://www.hhs.gov/ocr/civilrights/understanding/index.html>). Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see <http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html> (<http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html>). Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at <http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html> (<http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html>) or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at <http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53> (<http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53>).

### **Cooperative Agreement Terms and Conditions of Award**

Not Applicable

### **3. Reporting**

When multiple years are involved, awardees will be required to submit the [Research Performance Progress Report \(RPPR\)](http://grants.nih.gov/grants/rppr/index.htm) (<http://grants.nih.gov/grants/rppr/index.htm>) annually and financial statements as required in the [NIH Grants Policy Statement](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11161). ([http://grants.nih.gov/grants/guide/url\\_redirect.htm?id=11161](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11161))

A final RPPR, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the [NIH Grants Policy Statement](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11161) ([http://grants.nih.gov/grants/guide/url\\_redirect.htm?id=11161](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11161)).

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at [www.fsr.gov](http://www.fsr.gov) ([http://grants.nih.gov/grants/guide/url\\_redirect.htm?id=11170](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11170)) on all subawards over \$25,000. See the [NIH Grants Policy Statement](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11171) ([http://grants.nih.gov/grants/guide/url\\_redirect.htm?id=11171](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11171)) for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than \$10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently FAPIIS). This is a statutory

requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

## Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

### Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons, application errors and warnings, documenting system problems that threaten on-time submission, and post-submission issues)

Finding Help Online: <http://grants.nih.gov/support/> ([//grants.nih.gov/support/](http://grants.nih.gov/support/)) (preferred method of contact)

Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

General Grants Information (Questions regarding application processes and NIH grant resources)

Email: [GrantsInfo@nih.gov](mailto:GrantsInfo@nih.gov) (<mailto:GrantsInfo@nih.gov>) (preferred method of contact)

Telephone: 301-945-7573

Grants.gov Customer Support (Questions regarding Grants.gov registration and Workspace)

Contact Center Telephone: 800-518-4726

Email: [support@grants.gov](mailto:support@grants.gov) (<mailto:support@grants.gov>)

### Scientific/Research Contact(s)

Alice Chen, M.D.

National Center for Advancing Translational Sciences (NCATS)

Telephone: 301-827-2015

Email: [alice.chen2@nih.gov](mailto:alice.chen2@nih.gov) (<mailto:alice.chen2@nih.gov>)

### Peer Review Contact(s)

Carol Lambert, Ph.D.

National Center for Advancing Translational Sciences (NCATS)

Telephone: 301-435-0814

Email: [lambert@mail.nih.gov](mailto:lambert@mail.nih.gov) (<mailto:lambert@mail.nih.gov>)

### Financial/Grants Management Contact(s)

Stephanie Blackford

National Center for Advancing Translational Sciences (NCATS)

Telephone: 301-402-6737

Email: [Stephanie.Page@nih.gov](mailto:Stephanie.Page@nih.gov) (<mailto:Stephanie.Page@nih.gov>)

## Section VIII. Other Information

Recently issued trans-NIH [policy notices](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11163) ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11163](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11163)) may affect your application submission. A full list of policy notices published by NIH is provided in the [NIH Guide for Grants and Contracts](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11164) ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11164](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11164)). All awards are subject to the terms and conditions, cost principles, and other considerations described in the [NIH Grants Policy Statement](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11120) ([//grants.nih.gov/grants/guide/url\\_redirect.htm?id=11120](http://grants.nih.gov/grants/guide/url_redirect.htm?id=11120)).



## Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75.

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[Weekly TOC for this Announcement \(/grants/guide/WeeklyIndex.cfm?10-05-18\)](/grants/guide/WeeklyIndex.cfm?10-05-18)

[NIH Funding Opportunities and Notices \(/grants/guide/index.html\)](/grants/guide/index.html)

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