Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)

National Institutes of Health (NIH (http://www.nih.gov))

Components of Participating Organizations

National Institute of Neurological Disorders and Stroke (NINDS (http://www.ninds.nih.gov/))
National Center for Advancing Translational Sciences (NCATS (http://ncats.nih.gov/))

Funding Opportunity Title

Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases (U01 Clinical Trial Not Allowed)

Activity Code

U01 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=u01&Search.x=0&Search.y=0&Search_Type=Activity) Research Project – Cooperative Agreements

Announcement Type

Reissue of PAR-18-534 (https://grants.nih.gov/grants/guide/pa-files/par-18-534.html)

Related Notices

- **March 10, 2020** - Reminder: FORMS-F Grant Application Forms & Instructions Must be Used for Due Dates On or After May 25, 2020- New Grant Application Instructions Now Available. See Notice NOT-OD-20-077 (/grants/guide/notice-files/NOT-OD-20-077.html).
- **August 23, 2019** - Clarifying Competing Application Instructions and Notice of Publication of Frequently Asked Questions (FAQs) Regarding Proposed Human Fetal Tissue Research. See Notice NOT-OD-19-137 (/grants/guide/notice-files/NOT-OD-19-137.html).
- **July 26, 2019** - Changes to NIH Requirements Regarding Proposed Human Fetal Tissue Research. See Notice NOT-OD-19-128 (/grants/guide/notice-files/NOT-OD-19-128.html).

Funding Opportunity Announcement (FOA) Number

PAR-19-220

Companion Funding Opportunity

None

Number of Applications

See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.853, 93.350

Funding Opportunity Purpose

This Funding Opportunity Announcement (FOA) invites researchers to submit applications for support of clinical studies that address critical needs for clinical trial readiness in rare neurological and neuromuscular diseases. These studies should result in clinically validated biomarkers and clinical outcome assessment measures appropriate for use in upcoming clinical trials. Through the support of trial readiness studies, NINDS and NCATS expect to enhance the quality and increase the likelihood of success of clinical trials in these rare diseases.

Key Dates

Posted Date

March 13, 2019

Open Date (Earliest Submission Date)

July 14, 2019

Letter of Intent Due Date(s)

30 days prior to application due date.

Application Due Date(s)

August 14, 2019; February 19, 2020; August 19, 2020; February 17, 2021; August 18, 2021; February 16, 2022

by 5:00 PM local time of applicant organization. All types of non-AIDS applications 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.

AIDS Application Due Date(s)

Not Applicable

Scientific Merit Review

October/November 2019, June/July 2020, October/November 2020, June/July 2021, October/November 2021, June/July 2022

Advisory Council Review

January 2020, October 2020, January 2021, October 2021, January 2022, October 2022

Earliest Start Date

April 2020, December 2020, April 2021, December 2021, April 2022, December 2022

Expiration Date

February 17, 2022

Due Dates for E.O. 12372

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 (//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/)).

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 (/grants/guide/ApplyButtonSplash.cfm?dest=https://public.era.nih.gov/commons/) to track your application. Check with your institutional officials regarding availability.

3. Use Grants.gov (/grants/guide/ApplyButtonSplash.cfm?dest=GrantsGov&oppNum=PAR-19-220) Workspace to prepare and submit your application and eRA Commons (/grants/guide/ApplyButtonSplash.cfm?dest=http://public.era.nih.gov/commons/) to track your application.

Table of Contents

Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Purpose

The purpose of this FOA is to fill gaps in clinical trial readiness for rare neurological and neuromuscular conditions that will soon have candidate therapeutics ready to test in clinical trials, but, due to the lack of validated clinical outcome assessment (COA) measures or biomarkers, the success of those trials may be compromised. This FOA invites researchers to submit applications for support of multi-site, prospective clinical projects that address critical needs for clinical trial readiness in these conditions. For this FOA, clinical trial readiness is defined as having established clinically valid biomarkers and clinical outcome assessment (COA) measures that are fit-for-purpose within a defined context of use in a planned clinical trial or trials, and clinical validation of these research tools is the final step before their implementation in trials. The National Institute of Neurological Disorders and Stroke (NINDS) and the National Center for Advancing Translational Sciences (NCATS) intend to enhance the quality and increase the likelihood of success of upcoming clinical trials in these diseases by supporting studies leading to trial readiness.

The initiative will promote partnerships among academic investigators, industry, and patient groups, and will encourage interactions with the Food and Drug Administration (FDA).

Terminology?

This FOA uses terminology to describe this type of research as defined in the BEST (Biomarkers, EndpointS, and Other Tools (https://www.ncbi.nlm.nih.gov/books/NBK326791/)) Resource, 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 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 is intended to capture (or reflect).

Validation – A process to establish that the performance of a 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 in response 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 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 acceptably identifies, measures or predicts the 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 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.

Background

The NINDS and NCATS support basic, translational and clinical research on a broad range of diseases that are defined as rare; diseases affecting fewer than 200,000 individuals in the United States (per the Rare Diseases Act of 2002). Clinical trials employ biomarkers and/or COA measures to determine whether interventions are safe, efficacious or effective in the study cohort(s). As defined above, COAs are measures of how a person feels, functions or survives, and biomarkers are characteristics of biological or pathological processes, or responses to interventions. Examples of COA measures for rare neurological or neuromuscular diseases are tests of motor function, cognitive ability or behavior. Biomarkers used in clinical trials can be categorized as predictive, prognostic or pharmacodynamic/response, depending on what is measured and how the data will be used in the trial. Examples of pharmacodynamic/response biomarkers for rare neurological or neuromuscular diseases are levels of disease relevant proteins in cerebrospinal fluid, or magnetic resonance imaging or spectroscopy approaches to measure the structure or composition of regions of the nervous system. Prior to launching clinical trials, the biomarker assays must be analytically validated, and the biomarker and COA measures must be clinically validated to establish their accuracy, sensitivity and reliability. Without appropriately validated research tools, clinical trials may be inconclusive or misleading. For some of the rare diseases within the mission of NINDS, preclinical translational research has resulted in the development of candidate therapeutics that may soon be ready for testing in trials, but clinical trial readiness may be lagging. The limited number of participants available for clinical trials in rare diseases places especially high demands on the sensitivity of biomarker and COA measures used to assess response to interventions. For these reasons, clinical trial readiness is considered a high research priority for rare neurological and neuromuscular diseases.

FDA published Draft Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf) on common issues in drug development for rare diseases. We encourage investigators to follow this guidance while developing a clinical trial readiness study.

Scope

Diseases appropriate for this FOA should 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. Applications should propose clinical studies that verify that candidate COA measures and, if appropriate, biomarkers are optimized and ready for implementation within their context of use in upcoming trials. The applications should include a section (described below) that indicates what clinical trial(s) are being planned in the rare disease being studied. The project proposed must be necessary to achieve clinical trial readiness for the upcoming trial(s). Furthermore, when combined with existing clinical research tools and other ongoing research efforts, the proposed studies must be sufficient to fill the needs for validated biomarkers and COA measures for the upcoming trial(s) described in the application. 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).

Because of the large number of rare diseases within the mission of the NINDS and limited funds for this program, it is unlikely that more than one study will be funded for any disease. Therefore, investigators are encouraged to form collaborations with other researchers in the same disease area; reach consensus on the biomarkers and COA measures needing validation for use in upcoming clinical trials; and submit one application, rather than competing or complimentary applications.

Applications responsive to this FOA must propose multisite, prospective clinical studies aimed at validating COA measures or scales and may also propose clinical validation of biomarkers. Studies proposing only biomarker validation should consider applying to the NINDS FOAs on biomarker clinical validation (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/Neuro-Biomarkers).

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

- Studies aimed at the validation of clinician-reported, observer-reported, patient-reported, and/or performance outcomes with defined contexts of use in specific rare disease populations.
- Studies aimed at the validation of COA measures and one or more biomarker(s) that can be of any category relevant to clinical trials including safety, predictive, prognostic or pharmacodynamic/response.
- Studies to validate candidate biomarkers by analyzing the correlation of biomarkers with COA measure data collected in the same cohort.
- Studies that, through the validation of COA measures or biomarkers, collect the data necessary to determine appropriate participant inclusion/exclusion criteria for upcoming clinical trials.
- Studies that, through the validation of COA measures or biomarkers, collect the data needed for accurate power calculations or determining the appropriate duration of upcoming clinical trials.
- Validation studies that demonstrate responsiveness of biomarkers or COAs through the observation of patients who are receiving treatment as part of their clinical care.
- Ancillary studies that aim to validate COA measures or biomarkers by adding them to ongoing clinical studies (or trials) 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:

- Applications that propose animal studies will not be considered for funding.
- This FOA will not accept applications that propose clinical trials.
- Studies of biomarker discovery or early characterization should seek funding through the parent FOAs for research project grants.
- Studies of disease pathophysiology, genetic or epigenetic mechanisms are outside the scope of this FOA.
- 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 analytical validation.
- Applications that propose only to maintain patient registries will not be considered for funding. NINDS and NCATS 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 (e.g. the Rare Disease Clinical Research Network (RDCRN (https://ncats.nih.gov/rdcrn))).

This FOA will support well justified applications for testing of biomarkers or outcome measures, which include justification that assays and methods for measurement are ready for use in a multi-site study at the time of application. For biochemical or molecular biomarkers, this justification should describe 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 well-justified candidate biomarkers, and based on data

acquired during the study, be narrowed down to one or a few appropriate biomarkers to validate for use in a clinical trial.

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://ncats.nih.gov/rdcrn), NeuroNEXT (https://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/). Applicants should consider using the services of BioSEND (https://biosend.org/index.html) to bank and distribute biological specimens collected from participants in these trial readiness studies. Leveraging the resources and support from advocacy groups, private research foundations, academic institutions, other government agencies, and the NIH Intramural program are also encouraged.

Studies are also encouraged to leverage the resources of ongoing clinical trials or longitudinal studies supported through other Federal or private funds. Researchers may consider collecting data to validate new or improved COA measures or biomarkers as ancillary studies to ongoing clinical trials or longitudinal studies.

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument

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

Application Types Allowed

New
Resubmission

The OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116) and the SF424 (R&R) Application Guide provide details on these application types.

Clinical Trial?

Not Allowed: Only accepting applications that do not propose clinical trials
Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)

Funds Available and Anticipated Number of Awards

The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.

Award Budget

Application budgets are limited to $650,000 in direct costs in any project year (exclusive of facilities and administrative costs of subcontractors with collaborating organizations).

Award Project Period

The maximum project period is 5 years.

NIH grants policies as described in the NIH Grants Policy Statement (//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)
- 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
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply

Non-domestic (non-U.S.) components of U.S. Organizations **are** eligible to apply.

Foreign components, as defined in the *NIH Grants Policy Statement* (//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) 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) - 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/) (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 (//grants.nih.gov/grants/guide/url_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 (//grants.nih.gov/grants/guide/url_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. (//grants.nih.gov/grants/guide/url_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 (//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 (//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 (//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:

Glen H. Nuckolls, Ph.D.
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-5745
Email:glen.nuckolls@nih.gov) (mailto:glen.nuckolls@nih.gov)

Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits (//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.
Senior/key persons should have clinical research expertise for the rare disease under study.

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:
Rare Disease Status - The Significance section of the Research Strategy must include a paragraph with the heading "*Justification of Rare Disease*". This section should provide a justification that the disease/condition being studied is rare in the U.S. This section may include one or more references confirming that the prevalence of the disease/condition that is the primary focus of the research application is 200,000 or fewer patients in the U.S. If the disease/condition has been granted orphan status by the FDA, provide this information in the justification. If it is a rare variant or subset of a more common condition, provide a justification 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 must also include a further 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) 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. Provide letters of support (below) from the researchers who expect to conduct upcoming trials.
- 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.
- Briefly describe the role of companies or voluntary health organizations that are currently engaged or potentially available to contribute to 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 must contain a subsection with the heading "*Biomarkers and Their Contexts of Use*". This section should describe each biomarker that will be tested for validation and the context of use (COU). The COU should briefly 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 must 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 the time course of the disease is expected to show (e.g., linearly decreasing measurement, periodic fluctuations, etc.) and the expected relationship of the biomarker to COA measures.

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 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

COA measures can be clinician-, observer-, or patient-reported, or performance outcomes. Applications must 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.

Statistical Analysis Plans

A section describing the plans for statistical analysis of the data and tests for validation of biomarkers/COA (s) must be included in the application. Explain the decision for selecting the statistical analysis methods and how the methods selected are best suited for this rare disease study—what methods were considered; why were the proposed methods chosen. Describe sample size considerations for validating the biomarkers and COA(s). 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)

Advisory Committee

The Approach section of the Research Strategy must include a further subsection with the heading "*Advisory Committee*". This subsection should describe plans for establishing an advisory committee for the study, composed of at least five members. The members should include researchers not directly involved in the study, either from academics or from industry, who may lead future clinical trials that would be enabled by this trial readiness study. Researchers conducting similar studies in other diseases may also have the appropriate expertise for this committee. This subsection should also describe plans for an initial meeting of study investigators with the committee to seek comments and suggestions on the design of the study and approval of the study protocol, before enrollment begins. Also, describe plans for regular meetings with the committee to review progress and solicit advice on course corrections. Describe how the advice from the committee will be incorporated into the management of the study. The Advisory Committee will not be responsible for data and safety monitoring (see Data and Safety Monitoring section below). The NIH Project Scientist for the Cooperative Agreement should be invited to participate in all meetings of the committee but would not be a voting member.

The perspectives of patients and other study participants or their parents/guardians should be considered in the design and conduct of the study to enhance recruitment and retention and minimize participant burden. The Advisory Committee should include one or more patients or patient advocates. Furthermore, researchers should solicit feedback from study participants and use this information to guide the study. Methods for soliciting feedback from the participants may include surveys, or conducting group listening sessions. The Approach section should describe plans for soliciting this input, the methods to be used, the frequency of collecting feedback from patients/participants, and how this information will be used in the management of the study.

Project Milestones and Timelines

In this subsection under Approach, applicants must describe milestones to be used for measuring success in achieving each of the research plan's aims. Specify the quantitative criteria for measuring success and related rationale. One or more milestones should be used for each aim. Specify the timeline for each milestone. There should be at least one milestone each year. Consider including an interim data analysis and provide quantitative criteria for go/no-go decisions for continuing the study of each biomarker and/or COA. This is especially encouraged for any invasive biomarkers such as those involving longitudinal lumbar punctures.

Examples of milestones include, but are not limited to the following:

- Go/no go decision points regarding biomarker or COA sensitivity, reliability and responsiveness
- Institutional Review Board (IRB) and other regulatory approvals (applicants are encouraged to use a central IRB)
- Certification of clinical sites regarding the training of personnel on the study protocol, calibration of instruments, implementation of data management and safety monitoring protocols, etc.
- Approval of the research protocol by the Advisory Committee
- Patient enrollment (including gender, race and ethnicity, children) and clinic visit milestones for each grant year.

For biomarker and COA measure validation investigators are encouraged to request a Critical Path Innovation Meeting (CPIM) with the FDA Center for Drug Evaluation and Research (CDER) for drug products, or other similar earlier interaction meetings with other FDA Centers, where applicable, to seek FDA input into the proposal validation or study proposal. If applicable, a CPIM meeting could be one of the study milestones.

Include a timeline that indicates IRB approval(s), meetings of the Advisory Committee, staging of patient visits, and expected completion for each of the milestones. Also describe the time frame of planning for clinical trials that will utilize the resulting products of the trial readiness study.

Applicants are encouraged to use a central IRB, rather than independent review at each participating institution.

Letters of Support

If appropriate, provide a letter of support from the leader(s) of the existing clinical research network that will conduct the trial readiness study that indicates the sites involved in the network, relevant resources and study infrastructure, and an estimate of the number of eligible, relevant rare disease patients accessible through the network. 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 and indicates the timeline of the parent study relative to the proposed ancillary study.

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. NINDS has identified CDEs for many clinical neurological/neuromuscular diseases and types of outcomes (e.g., patient-reported outcomes). NINDS provides resources for CDEs (https://www.commondataelements.ninds.nih.gov/#page=Default (https://www.commondataelements.ninds.nih.gov/#page=Default)) to assist investigators in developing protocols, case report forms, and other instruments for data collection. Investigators are encouraged to consult the NINDS CDE website and describe in their applications any use they will make of these CDEs in their projects.

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, are expected to include a plan for the sharing of clinical data and biospecimens, consistent with achieving the goals of the program.
- This Data/Resource Sharing Plan should include a timeline for publications and access to additional study data and biospecimens. 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. If using BioSEND (https://biosend.org/index.html), briefly describe how this resource will be used to bank and distribute biospecimens. A table of the requests should be included in annual progress reports and provided to the Advisory Committee, including the requester's name, nature of the request, date received, description and date of follow-through on each request.

Appendix:

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

- Standardized protocols for measuring the biomarkers or evaluating the COA proposed are required
- If an ancillary study is proposed, the protocol for the parent clinical trial or longitudinal study and the consent form for the parent study are required
- If the investigators have had communications with the FDA through a Critical Path Innovation Meeting or other meeting(s) about the proposed biomarker(s) or COA measure(s), a summary of the meeting or documentation of guidance from the FDA is required.
- If the proposed study involves the expanded access regulatory pathway, protocols used for expanded access studies or documentation submitted to FDA to initiate and amend expanded access protocols are required..

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.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11137), and procedures for foreign institutions described throughout the SF424 (R&R) Application Guide.

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) , 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) (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), 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)

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) .

Pre-award costs are allowable only as described in the NIH Grants Policy Statement (//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). 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). 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) 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.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in the policy (//grants.nih.gov/grants/guide/url_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. Applications submitted to the NIH in support of the NIH mission (//grants.nih.gov/grants/guide/url_redirect.htm?id=11149) are evaluated for scientific and technical merit through the NIH peer review system.

For this particular announcement, note the following:

Applications must contain the special subsections "Justification of Rare Disease" and "Urgent Need For Clinical Trial Readiness" under "Significance", and "Biomarkers And Their Contexts of Use", "Advisory Committee", and "Milestone And Timelines" under "Approach". Reviewers will consider special review criteria described below for each of these subsections.

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 the prior research that serves as the key support for the proposed project rigorous? 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 scientific justification 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)? If the study focuses on a rare subcategory of a common disease/condition, how strong is the justification for the need to address clinical trial readiness specifically for this subcategory?
- If the application is for a rare variant or subset of a more common condition, how strong is the justification that a separate clinical trial readiness activity is needed to focus on this rare form?
- How well does the project fill a gap in preparing for an upcoming clinical trial or trials. ? How does this application address a gap in outcome measure and/or biomarker clinical validation?
- 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 justification 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 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 included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed 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?

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 individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

Specific to this FOA:

- How well does the application describe plans to ensure that the study is scientifically rigorous, appropriately controlled to minimize bias, and reported with transparency regarding the data collected?
- How likely are the proposed studies to establish clinically validated biomarkers and/or COA measures with well-defined contexts of use in upcoming clinical trials?
- How well will the milestones measure success in achieving the aims of the application? How feasible are the milestones for participant enrollment relative to the timeline for completing the aims within the term of the grant?
- If an interim analysis is proposed, how effectively will the milestones for the performance of COA measures or biomarkers establish appropriate go/no-go decision points in preparing for clinical trials?
- How well prepared for use in this study are the assays for biochemical or molecular biomarkers, or the methods for measuring imaging, radiological or physiological biomarkers, and/or COAs?
- How well does the application describe a plan to establish and meet regularly with the Advisory Committee? Are there appropriate plans to incorporate the advice from this committee to the management of the study?
- How well does the application describe plans for including the comments of patients and other study participants or their parents/guardians in the management of study recruitment, retention and the minimization of participant burden?
- Is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results? Is the study appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group) and duration of the study, appropriate and well justified?
- Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate? Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate?
- Are the plans to standardize, assure quality of, and monitor adherence to, the study protocol and data collection appropriate? Does the application propose to use existing available resources, as applicable?
- Are planned analyses and statistical approach appropriate for the proposed study design given the limited number of participants eligible for this rare disease study? Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?
- Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate?
- Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

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?
- If proposed, are the administrative, data coordinating, enrollment and laboratory/testing centers, appropriate for the study proposed?
- Does the application adequately address the capability and ability to conduct the study at the proposed site(s) or centers? Are the plans to add or drop enrollment centers, as needed, appropriate?
- If international site(s) is/are proposed, does the application adequately address the complexity of executing the clinical study in accordance with policies and regulations at each site?
- Is there evidence of the ability of the individual sites to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and, (4) operate within the proposed organizational structure?

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 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 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).

Inclusion of Women, Minorities, and Individuals Across the Lifespan

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 individuals of all ages (including children and older adults) 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).

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).

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

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); (2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and (3) Genomic Data Sharing Plan (GDS) (//grants.nih.gov/grants/guide/url_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 the NINDS, in accordance with NIH peer review policy and procedures (//grants.nih.gov/grants/guide/url_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:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- 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 appropriate national Advisory Council for NINDS and/or NCATS. 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.
- Compliance with resource sharing policies

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 (//grants.nih.gov/grants/guide/url_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 (//grants.nih.gov/grants/guide/url_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).
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) 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) 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) 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). More information is provided at Award Conditions and Information for NIH Grants (//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 (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, 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

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the U01 cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the purpose of the NIH is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have primary responsibility for:

- Defining of research objectives and approaches.
- Planning, conducting, analyzing, and publishing results, interpretations, and conclusion of their studies and for providing overall scientific and administrative leadership for the Research Project.
- Supervising of the clinical study with consistent emphasis on collaborative interactions among PD(s)/PI(s), advisory and steering committees, and NIH representatives.
- Retaining custody of and maintaining primary rights to data and software developed under this award, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH Staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- NIH staff involvement will include oversight of the IRB-approved protocol by the NIH Program Official, documentation of adequate serious adverse event management and reporting, and regular communications with the PD/PI and staff; additional involvement generally includes participation in meetings of the advisory committee. Specifically:
- An NIH Project Scientist working with the PD/PI will develop milestones for the study. Failure to meet the agreed upon milestones may result in reduced funding or early termination of the cooperative agreement. The NIH retains the option to obtain periodic external peer review of progress.
- The NIH Project Scientist will function as one of several co-investigators, collaborating and interacting as necessary with the PD(s)/PI(s) in accomplishing the overall goals of the Research Program.
- In addition, an NIH Program Official will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice.
- The NIH Program Official and Project Scientist should also be invited to participate in meetings of the steering committee and the Scientific Advisory Committee.
- If the proposed study should involve interaction with the FDA regarding biomarkers or outcome measures, the NIH Project Scientist and/or Program Official(s) will be present at any meetings held with the FDA related to this NIH-funded protocol.

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.

As with any award, even during the period recommended for support, continuation is conditional upon satisfactory progress. If, at any time, recruitment falls significantly below the projected milestones for recruitment, the NIH will consider ending support and negotiating a phase-out of the award. The NIH retains the option to obtain periodic external peer review of progress. Milestones will be established by the NIH prior to the award of the grant based on recommendations from the primary review group. Feasibility milestones will be defined at the start of each trial and will be monitored closely by the NIH Program Official. Achievement of these milestones will be evaluated by NIH prior to releasing funding for each year of the award and failure to

achieve these milestones may lead to study termination.

Areas of Joint Responsibility include:

- Clarifying, negotiating, and finalizing the milestones and timelines.

Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the Steering Committee chosen without NIH Staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16. Final decisions made by NIH regarding a discontinuation are not appealable.

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) (//grants.nih.gov/grants/rppr/index.htm) annually and financial statements as required in the NIH Grants Policy Statement. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)
In addition to the information described in the RPPR instructions, awardees should also include the following information in each progress report:

- A summary of any recommendations from the Advisory Committee if a meeting occurred during the year of reporting.
- The Resource Sharing Plan should include a timeline for publications and access to additional study data and biospecimens. 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. If using BioSEND (https://biosend.org/index.html), briefly describe the process for evaluating request used by this resource. A table of the requests for study data or biospecimens received from other researchers including the requester's name, nature of the request, date received, description and date of follow-through on the requests.

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 (//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.fsrs.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11170) on all subawards over $25,000. See the NIH Grants Policy Statement (//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/) (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) (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)

Scientific/Research Contact(s)

Glen H. Nuckolls, Ph.D.
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-5745
Email:glen.nuckolls@nih.gov (mailto:glen.nuckolls@nih.gov)

Peer Review Contact(s)

Ernest Lyons, Ph.D.
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-9223
Email:Ernest.Lyons@nih.gov (mailto:Ernest.Lyons@nih.gov)

Financial/Grants Management Contact(s)

Chief Grants Management Officer
National Institute of Neurological Disorders and Stroke (NINDS)
Email: ChiefGrantsManagementOfficer@ninds.nih.gov (mailto:ChiefGrantsManagementOfficer@ninds.nih.gov)

Section VIII. Other Information

Recently issued trans-NIH policy notices (//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 (//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 (//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.

Weekly TOC for this Announcement (/grants/guide/WeeklyIndex.cfm?03-15-19)
NIH Funding Opportunities and Notices (/grants/guide/index.html)

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, Audio or Video files, see Help Downloading Files (/grants/edocs.htm).