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/))

Funding Opportunity Title

Comparative Effectiveness Research in Clinical Neurosciences (UG3/UH3 Clinical Trial Not Allowed)

Activity Code

UG3 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=ug3&Search.x=0&Search.y=0&Search_Type=Activity)/UH3 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=uh3&Search.x=0&Search.y=0&Search_Type=Activity) Exploratory/Developmental Phased Award Cooperative Agreement

Announcement Type

New

Related Notices

- **November 18, 2019** - Notice of Correction to the instructions for submitting applications to PAR-19-171. See Notice NOT-NS-20-019 (//grants.nih.gov/grants/guide/notice-files/NOT-NS-20-019.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-19-171

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

Funding Opportunity Purpose

The purpose of this Funding Opportunity Announcement (FOA) is to encourage grant applications for investigator-initiated prospective observational comparative effectiveness research (CER) to the National Institute of Neurological Disorders and Stroke (NINDS) (note: only prospective observational studies will be considered)). The study must address questions within the mission and research interests of the NINDS and may evaluate preventive strategies, diagnostic approaches, or interventions including drugs, biologics, and devices, or surgical, behavioral, and rehabilitation therapies. NINDS is particularly interested in pragmatic study designs that utilize a cost-effective means of prospectively collecting observational data important to current clinical practice.

Key Dates

Posted Date

January 28, 2019

Open Date (Earliest Submission Date)

February 27, 2019

Letter of Intent Due Date(s)

30 days prior to application due date.

Application Due Date(s)

New applications: March 29, 2019; June 18, 2019; October 18, 2019; February 19, 2020; June 18, 2020; October 14, 2020; February 18, 2021; June 18, 2021; October 14, 2021
, by 5:00 PM local time of applicant organization.

Resubmission or, Revision applications: April 30, 2019; July 18, 2019; November 14, 2019; March 18, 2020; July 14, 2020; November 18, 2020, March 18, 2021; July 14, 2021; November 18, 2021, by 5:00 PM local time of applicant organization.

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)

Standard AIDS dates (//grants.nih.gov/grants/guide/url_redirect.htm?id=11112) apply, by 5:00 PM local time of applicant organization. All types of AIDS and AIDS-related 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.

Scientific Merit Review

July 2019, November 2019, March 2020, July 2020, November 2020, March 2021, July 2021, November 2021, March 2022

Advisory Council Review

October 2019, January 2020, May 2020, October 2020, January 2021, May 2021, October 2021, January 2022, May 2022

Earliest Start Date

November 2019, February 2020, June 2020, November 2020, February 2021, June 2021, November 2021, February 2022, June 2022

Expiration Date

January 08, 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 (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-19-171) Workspace to prepare and submit your application and eRA Commons (http://public.era.nih.gov/commons/) to track your application.

Table of Contents

Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Background

The “gold standard” of evidence for establishing the utility and success of therapeutic interventions is the randomized clinical trial (RCT). However, challenges in the design and execution of definitive RCTs and obstacles to implementation of trial results often limit their use in specific settings. One example of an obstacle is the “ideal” context in which the trial is conducted (efficacy), rather than a “real world” setting (effectiveness) where the intervention would be implemented eventually. Even a well-designed efficacy RCT may be difficult to interpret because of exceptions from randomization, such as dropouts, cross-overs, or missing data. Given the high cost of traditional RCTs and their potential limitations, other approaches to developing rigorous evidence to support clinical decision-making are needed. One example of this approach is the prospective observational comparative effectiveness study.

The purpose of this funding opportunity announcement (FOA) is to encourage grant applications for investigator-initiated prospective observational comparative effectiveness studies. For the purposes of this FOA, comparative effectiveness research (CER) is defined as the conduct of research comparing the benefits and harms of different existing interventions and strategies to prevent, diagnose, treat and monitor health conditions in “real world” settings (modified from Federal Coordinating Council for Comparative Effectiveness Research. Report to the President and the Congress. US Department of Health and Human Services, 2009; https://osp.od.nih.gov/wp-content/uploads/FCCCER-Report-to-the-President-and-Congress-2009.pdf). The NINDS has a longstanding interest in CER. CER typically utilizes “real world” settings to compare existing interventions or strategies that have been studied individually in randomized controlled trials (RCT), that are commonly used clinically despite the absence of evidence from prior controlled trials, or that are used in settings where patients might have treatment preferences, despite equipoise among medical care providers. A comparative effectiveness approach may also be useful to:

1. determine the optimal patient population or situation for a given intervention;
2. determine outcomes when it is unethical, excessively costly, or not feasible to perform a RCT;
3. estimate specific parameters for study in a future RCT;
4. determine whether a specific treatment adds “value” (i.e., is cost effective), compared to standard of care treatments; or
5. determine outcomes that can be applied in registries where treatments or standard of care may change over time.

Broadly speaking, CER can be performed using a variety of methods, including prospective observational studies, clinical trials, or structured evaluation of existing evidence from registries, electronic health records, and other databases (e.g., meta-analyses, systematic reviews, modeling). An important component of CER is the application of analytical strategies, such as multivariable regression, propensity score analysis, and instrumental variable analysis, to adjust for known inherent biases resulting from lack of randomization.

For this FOA, only prospective observational studies will be considered for funding. Other types of CER studies may be submitted to other FOAs, if applicable. The grant mechanism used to support this funding announcement is a cooperative agreement (UG3/UH3) mechanism with two phases. The initial milestone-driven planning phase (UG3) will last for up to 2 years, with possible transition to a prospective observational study phase of up to 5 additional years (UH3). Only UG3 projects that have met scientific milestones and feasibility requirements will be approved to transition to the UH3 phase. The UG3/UH3 application must be submitted as a single application. The UG3 phase for observational studies will permit both scientific and operational planning activities. The UH3 phase of the award will support the conduct of investigator-initiated prospective observational studies.

The UG3 award (Planning Phase) will provide up to 2 years of support for scientific and operational planning activities required (not yet completed) to prepare for conduct of a subsequent CER study. The UH3 award (Implementation Phase) will provide up to 5 years of support for conduct of the CER study in accordance with

activities planned in the UG3 phase. This study should be hypothesis-driven, milestone-defined, and have the potential for high impact within the research mission of NINDS. The study must meet all applicable NIH and Office of Human Research Protections (OHRP) policy requirements.

UG3/UH3 Transition: At the completion of the UG3 planning phase, the applicant will be required to submit a detailed transition request to progress to the UH3 implementation phase. UH3 transition requests will undergo administrative review by NIH staff to determine whether the study will be awarded the implementation phase (UH3). Transition decisions will be based on achievement of study milestones, readiness to conduct the UH3 study, feasibility of completing the UH3 study, availability of funds, and program priorities.
Prospective applicants should note that initial funding of the UG3/UH3 cooperative agreement does not guarantee support of the UH3 implementation phase. UH3 funding is dependent on NINDS program priorities and availability of funds. In addition, applicants should understand that transition to the UH3 phase of the project will occur only if the administrative review process determines that the UG3 planning milestones have been successfully met and that the UH3 phase can proceed with confidence of success.

Additional Information
Each NINDS UG3/UH3 Cooperative Agreement application may only be used to propose the planning and implementation of a single observational study.
Studies of outcomes in populations that typically are subject to health disparities and under-representation in clinical trials (including, but not limited to, racial and ethnic minorities, persons with disabilities, children, the elderly, and patients with multiple chronic conditions) are particularly encouraged.

Diseases, disorders, and conditions that are considered to be under-researched (particularly with respect to burden of illness) are also encouraged.

Applicants should take note of the following special requirements and considerations:

1. *Scope*. The scope of this FOA includes prospective observational studies (for example, studies of typical care when multiple treatment modalities are used, natural experiments with changes in medical care or policies, studies where care differs based on geography, or cohort-based studies, among others).
2. The following types of studies are considered out of scope for this FOA:

- Clinical trials, including network-based studies (e.g., NeuroNEXT, StrokeNet, or SIREN). For a list of NINDS clinical trial Funding Opportunity Announcements, see https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research)
- Pooled secondary analyses of existing large databases and/or cohorts, meta-analyses, systematic reviews, and simulations (applicants should consider applying under PA-18-484 or PA-18-358)
- Dissemination and implementation research (applicants should consider applying under PAR-16-238)
- Systematic reviews or meta-analyses of existing clinical trials. For this type of study, applicants should consider applying under PA-18-484 or PA-18-358, as appropriate.

3. *Relationships with Patient Groups*: Applicants are strongly encouraged to establish relationships with patient groups and solicit their input on recruitment, the clinical meaningfulness of the question under study, the relevance of the proposed clinical outcomes, and approaches to minimizing the burden on study subjects.

4. *IRB documentation*: IRB approval of the protocol and informed consent are not required at the time of application submission unless the UG3 phase involves human subjects; it is required prior to UH3 (Implementation Phase) funding.Applications should comply with the NIH Single IRB Policy for multi-site research, if applicable (https://grants.nih.gov/policy/clinical-trials/single-irb-policy-multi-site-research.htm). NINDS encourages investigators to begin these processes as early as possible. NINDS also will require documentation of any other necessary regulatory approvals (e.g., Recombinant DNA Advisory Committee) prior to funding, if applicable.

5. *NIH Resources*: As appropriate, applicants are encouraged to make use of the following resources for clinical research including:

- NINDS Common Data Elements (https://www.commondataelements.ninds.nih.gov/#page=Default).
- Clinical and Translational Science Award (CTSA) program (https://ctsacentral.org/);
- NeuroQOL (http://www.healthmeasures.net/explore-measurement-systems/neuro-qol);
- NIH Toolbox (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox);
- PROMIS (http://www.healthmeasures.net/explore-measurement-systems/promis); and

6. Innovative Technologies: Applicants are encouraged to consider utilizing (at least experimentally) digital/mobile/sensor technologies and web-based systems to facilitate data collection (including data collection in a continual, contextual, real-world setting) and to enhance protocol adherence.Innovative statistical approaches are also encouraged, when appropriate.

7. Consultation with NINDS: Applicants are strongly encouraged to consult with NINDS Scientific/Research staff before an application is developed (see Section VII, Agency Contacts), but no later than 12 weeks prior to the anticipated application submission date .This early contact will provide an opportunity to clarify NINDS policies and guidelines as well as to discuss how to develop an appropriate project timeline and milestone plan, which is subject to peer review. The NINDS considers program priorities and scientific overlap with other funded projects. Scientific/Research contacts are also available to discuss strategies for recruitment and inclusion of women and minorities.

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
Revision
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 not limited but need to reflect the actual needs of the proposed project.

Award Project Period

Up to 2 years for the UG3; up to 5 years for the UH3.

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)
- Eligible Agencies of the Federal Government
- 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/) – 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)NIH Grants Policy Statement. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)

3. Additional Information on Eligibility

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

The application forms package specific to this opportunity must be accessed through ASSIST, Grants.gov Workspace or an institutional system-to-system solution. Links to apply using ASSIST or Grants.gov Workspace 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:

Adam L. Hartman, MD
Telephone: 301-496-9135
E-mail: adam.hartman@nih.gov (mailto:adam.hartman@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.

R&R 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:

Significance: Because of the nature of CER (i.e., a comparison of treatments), there should be a justification for selection of the proposed interventions from amongst the many available options. Because the goal is to target effectiveness (i.e., "real-world" environment with few inclusion/exclusion criteria) rather than efficacy (i.e., ideal conditions with limited numbers of patients with strict inclusion/exclusion criteria), the proposed study should have the potential to inform decisions by key stakeholders, including patients, clinicians, and/or policymakers. Study outcomes should target the intended population for the intervention because of the "real world" nature of the investigation. Similarly, the application should address priorities articulated by patients, clinicians, and/or policymakers and the priorities of these groups should be gauged prior to submission and reported in the application. The application should address an area of need, such as an underserved population or disease entity.

Investigator(s): The investigator team should be qualified in terms of experimental design, study execution, data handling, and statistical analyses/interpretation of CER-derived data. For a multicenter study, the organizational structure should be appropriate and the application should identify a core of potential center investigators and staffing for a clinical and data coordinating center.

UG3 Approach: The application should include descriptions of the following:

1. Processes for including proposed international clinical sites, if applicable.
2. Data management system and case report forms, incorporating applicable NINDS Common Data Elements;
3. Development of tools for data and quality management;

UH3 Approach: The application should discuss the following:

1. Enrollment, retention, plans to minimize losses to follow-up, and acceptable attrition rates;
2. Plans for site activation, execution of contracts and training of additional clinical sites, including any international sites, if applicable;
3. Because interventions proposed for study in this CER FOA already have been used in practice or already studied in efficacy trials, a description of optimal use of existing data that serve as the background/rationale for the study;
4. Safety monitoring, which may include a Medical Monitor, Study Monitoring Committee, or an Observational Study and Monitoring Board, when appropriate.
5. A clear (and when appropriate, innovative) analysis plan, and if applicable, a decision rule that will allow a clinically-relevant and focused recommendation at the end of the study;
6. If applicable, the decision rule that accounts for efficacy and safety, thus addressing the optimal benefit vs. risk;

7. Data quality and quality assurance, including a description of how missing data will be handled;
8. If using a noninferiority design, the noninferiority margin and justification for that margin;
9. A critical assessment of the implications of study results in terms of the statistical limits (i.e., probability distribution) of the data;
10. If proposing multisite recruitment or using recruitment from different sources (e.g., different cohorts), a description of how these populations differ;
11. Potential confounders (i.e., appropriate analyses should be proposed to account for potential confounders, including a propensity analysis, risk-adjusted regression, or instrumental variable analysis, etc.);
12. If applicable, a plan to use NINDS common data elements and a plan to allow harmonization of outcomes with similar existing or future projects.

Environment: Statistical support should be adequate to manage the data and analyses required for CER. There should be a clear plan for management of a multisite team, if applicable.

Study timeline and milestones:

UG3: The application should specify the timeline of the following milestones, which need to be completed before approval to enter the UH3 phase:

1. Development of recruitment and retention strategies
2. Development of data management system and case report forms, incorporating applicable NINDS Common Data Elements;
3. Development of tools for data and quality management;
4. Finalization of protocol, manual of procedures, consent forms, and data management plan;
5. Finalization of planned analyses (including interim analyses, if appropriate);
6. Protocol approval from a Medical Monitor, Study Monitoring Committee, or an Observational Study and Monitoring Board, when appropriate;
7. Initiation of contracts and training of clinical site personnel (NINDS expects the initiation of all study sites to occur in the start-up stage; if a large number of sites is needed, a plan that describes how additional sites will be added after the initiation of the study should be included);
8. Initiation of processes for including proposed international clinical sites, if applicable;
9. Plans for site activation, execution of contracts and training of additional clinical sites, including any international sites, if applicable.

UH3: The application should specify the timeline of the following milestone:

1. Interim (if applicable) and final data analyses.

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.

Appendix:

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

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
Note: Delayed onset does NOT apply to a study that can be described but will not start immediately (i.e., delayed start).

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11142)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. 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. 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.

Requests of $500,000 or more for direct costs in any year

Applicants requesting $500,000 or more in direct costs in any year (excluding consortium F&A) must contact a Scientific/ Research Contact at least 6 weeks before submitting the application and follow the Policy on the Acceptance for Review of Unsolicited Applications that Request $500,000 or More in Direct Costs as described in the SF424 (R&R) Application Guide.

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 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.

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?

Because of the nature of CER, is there good justification for selection of the proposed interventions (from amongst the many available options)? Because the goal is to target effectiveness (rather than efficacy), does the proposed study have the potential to inform decisions by key stakeholders, including patients, clinicians, and/or policymakers? Will study outcomes target the intended population for the intervention? Is the application responsive to priorities articulated by patients, clinicians, and/or policymakers? Have the priorities of these groups been gauged prior to submission? Does the application address an area of need, such as an underserved population or disease entity?

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?

Is the investigator team qualified in terms of experimental design, study execution, data handling, and statistical analyses/interpretation of CER-derived data?
For a multicenter trial, is the organizational structure appropriate and does the application identify a core of potential center investigators and staffing for a coordinating center?

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?

Are the analysis plan and statistical approach innovative?

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?

Because interventions proposed for study in this CER FOA already have been used in practice or already studied in efficacy trials, is there optimal use of existing data that serve as the background/rationale for the study? Is there a clear analysis plan, and if applicable,a decision rule that will allow a clinically-relevant and focused recommendation at the end of the study? If applicable, does the decision rule account for efficacy and safety, thus addressing the optimal benefit vs. risk? Does the application describe data quality and quality assurance,how missing data will be handled, and acceptable attrition rates? If using a noninferiority design, are the noninferiority margin and justification for that margin described? Are implications of study results assessed critically in terms of the statistical limits (i.e., probability distribution) of the data? If proposing multisite recruitment or using recruitment

from different sources (e.g., different cohorts), does the application describe how these populations differ? Are potential confounders considered (i.e., are appropriate analyses proposed to account for potential confounders, including a propensity analysis, risk-adjusted regression, or instrumental variable analysis, etc.)? If applicable, does the application propose to use NINDS common data elements , and is there a plan to allow harmonization of outcomes with similar existing or future projects?

Does the application adequately address the following, if applicable:

Study Design
Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/premise of the study based on previously well-designed preclinical and/or clinical research? 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), proposed intervention arms/dose, 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 differences addressed, if applicable, in the intervention effect due to sex/gender and race/ethnicity?

Are the plans to standardize, assure quality of, and monitor adherence to, the study protocol and data collection or distribution guidelines appropriate? If appropriate, is there a plan to assure ongoing access to treatments proposed throughout the study period? Does the application propose to use existing available resources, as applicable?

Data Management and Statistical Analysis
Are planned analyses and statistical approach appropriate for the proposed study design and methods? 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 to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

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?

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?

Are resources for statistical support adequate to manage the data and analyses required for CER?

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 study?

If multi-sites/centers, is there evidence of the ability of the individual site or center 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.

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)? Are the UG3 and UH3? milestones specific, measurable, attainable, realistic, and timed appropriately?

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

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

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), 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 or Board. 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 (//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 https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/index.html. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see https://www.hhs.gov/civil-rights/for-individuals/section-1557/index.html; and https://www.hhs.gov/civil-rights/for-providers/laws-regulations-guidance/index.html. Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see https://www.hhs.gov/civil-rights/for-individuals/disability/index.html. Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at https://www.hhs.gov/ocr/about-us/contact-us/index.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.

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 75 and other HHS, PHS and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, and "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 NIH purpose 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 the primary responsibility for:

- The Program Director/Principal Investigator will have the primary responsibility to define research objectives and approaches and to plan, conduct, analyze and publish results, interpretation and conclusions of their studies and for providing overall scientific and administrative leadership for the research project.
- The PD/PI will oversee all aspects of the organization and execution of the studies outlined in the application and approved by NINDS after peer review.
- Awardees have primary and lead responsibilities for the project as a whole, including any modification of study design, conduct of the study, quality control, data analysis and interpretation, preparation of publications, and collaboration with other investigators, unless otherwise provided for in these terms or by action of the primary leadership committee.
- Awardees will be responsible for reporting recruitment data to the NINDS Recruitment Planning & Monitoring System (RPMS).
- Awardees will be responsible for putting all study materials and procedure manuals into the public domain. Awardees are expected to publish and publicly disseminate results, data and other products of the study, concordant with governance policies and protocols. Publications and oral presentations of work performed under this agreement will require appropriate acknowledgement of support by the NINDS/NIH.
- Awardees will be responsible for obtaining prior written approval of the NINDS Grants Management Specialist in consultation with the NINDS Program Officer for any change in any of the key personnel identified in the Notice of Grant Award.

Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies.

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

An NINDS Project Scientist will have substantial programmatic involvement that is above and beyond the typical stewardship role in other awards, as described below. In addition to the Project Scientist, an NINDS Administrative Program Director will be responsible for programmatic stewardship of the award and will be named in the award notice. This stewardship will include detailed monitoring of trial progress and milestones as described below. A third NINDS Program Official from the Office of Clinical Research will serve as the NINDS liaison to the NINDS appointed Data and Safety Monitoring Board.

The NINDS Project Scientist will:

- Have access to data generated under this Cooperative Agreement and may periodically review the data and administrative progress reports. Program staff may use information obtained from the data for the preparation of internal reports on the activities of the study. However, awardees will retain custody of and have primary rights to all data developed under these awards, subject to Government rights of access consistent with HHS, PHS, and NIH policies.
- Serve as a resource to provide scientific/programmatic support during the accomplishment of the research by participating in the design of the activities, advising in the selection of sources or resources (e.g., determining where a particular reagent can be found), provision of research resources and reagents available from NINDS grantees and contractors, advising in management and technical performance, or participating in the preparation of publications.
- Oversee the adequacy of adverse event management and reporting, and have regular communications with the PD/PI and study team, which may include attendance at the DSMB and related committee meetings.
- Review the progress of the study, and of each participating facility, through consideration of the annual reports, site visits, screening logs, etc. This review may include, but is not limited to, compliance with the study protocol, meeting enrollment targets, adherence to uniform data collection procedures, and the timeliness and quality of data reporting.
- Monitor progress of study milestones; as with any award, continuation, even during the period recommended for support, is contingent upon satisfactory progress. Progress will be monitored by NINDS. The schedule for these interim reviews will be based upon the duration of the clinical trial period. Continuation of funding will be dependent upon the awardee’s ability to show adequate progress

towards milestone accomplishment.

- Compare, at each scheduled interim review, actual enrollment to the benchmarks and criteria identified in the application and negotiated prior to award. Awardees who do not accomplish the negotiated milestones shall submit a milestone report which will include a discussion of why the milestones were not met in the agreed upon timeframe and propose a corrective recruitment action plan. The corrective recruitment action plan shall include: amended milestones, plans to achieve the amended milestones and any additional items required by Program staff. The plan shall be provided to Program staff no later than 2 months following the missed milestone. Studies in which recruitment milestones are not met as per criteria established pre-award, or for which regulatory approval has not been met within one year, and are unlikely to improve sufficiently to bring the study to completion within an acceptable budget or time frame, may be closed for lack of progress. If NINDS or the awardee concludes that the study is no longer feasible, the investigator will be required to submit a close-out plan to NINDS within 2 months. The plan must be approved and signed by the Institutional Officials and the PI/PD(s) listed on the awards prior to submission.

NINDS reserves the right to terminate or curtail the study (or an individual award) under a range of scenarios including but not limited to (a) failure to implement the study protocol, (b) a substantial shortfall in subject recruitment, follow-up, data reporting and dissemination, quality control, or other major breach of the protocol, (c) substantive changes in the agreed-upon protocol with which NINDS does not concur, (d) reaching a major study objective substantially ahead of schedule with persuasive statistical evidence, (e) human subject safety or ethical issues that may dictate a premature termination, or (f) a change in the state of science that changes equipoise or has other significant impact on the relevance of the question.

Areas of Joint Responsibility include:

- The NINDS Project Scientist will serve on the primary leadership committee. In addition, the Project Scientist, or other NINDS Program Officials, may serve on other study committees regarding recruitment, intervention, follow-up, quality control, protocol adherence, assessment of problems affecting the study and potential changes in the protocol, interim data and safety monitoring, final data analysis and interpretation, preparation of publications, and development of solutions to major problems such as insufficient participant enrollment. The NINDS Project Scientist will have voting membership on the primary leadership committee and its subcommittees.
- Each full member will have one vote. Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.

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: 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 individual 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.

Continuation of Funding:

The award and administrative continuation of funding are subject to milestones to be specified in the notice of grant award according to NINDS policies (see NINDS policy for continuation of Phase 3 clinical trials (NOT-NS-10-009 (https://grants.nih.gov/grants/guide/notice-files/NOT-NS-10-009.html)). The Terms and Conditions will include site activation and recruitment milestones, accrual goals for women and minorities (as appropriate) and any other identified requirements for completion of the approved research.

As with any award, continuation is conditional upon satisfactory progress, even during the period recommended for support. If recruitment falls significantly below the projected milestones at any time, the NINDs may consider ending support and implementing a phase-out of the award. The NINDS retains the option to obtain periodic external peer review of progress.

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)
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)

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Financial/Grants Management Contact(s)

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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?02-01-19)
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).