

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)

National Institutes of Health ([NIH](#))

Components of Participating Organizations

National Institute of Neurological Disorders and Stroke ([NINDS](#))

Funding Opportunity Title

NIH StrokeNet Clinical Trials and Biomarker Studies for Stroke Treatment, Recovery, and Prevention (U01)

Activity Code

[U01](#) Research Project – Cooperative Agreements

Announcement Type

Reissue of [PAR-14-220](#)

Related Notices

None

Funding Opportunity Announcement (FOA) Number

PAR-17-274

Companion Funding Opportunity

[PAR-17-275](#), U44, Small Business Innovation Research (SBIR) Cooperative Agreement

[PAR-17-277](#), X01 Resource Access Award

Number of Applications

See [Section III. 3. Additional Information on Eligibility](#).

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

93.853

Funding Opportunity Purpose

This FOA encourages applications for multi-site exploratory and confirmatory clinical trials focused on promising interventions, as well as biomarker-or outcome measure validation studies that are immediately preparatory to trials in stroke prevention, treatment, and recovery. Successful applicants will collaborate and conduct the trial within the NIH StrokeNet. Following peer review, NINDS will prioritize trials among the highest scoring to be conducted in the NIH StrokeNet infrastructure. The NIH StrokeNet National Coordinating Center (NCC) will work with the successful applicant to implement the proposed study efficiently and the National Data Management Center (NDMC) will provide statistical and data management support. The NIH StrokeNet Regional Coordinating Centers (RCCs) and their affiliated clinical sites will provide recruitment/retention support as well as on-site implementation of the clinical protocol.

The NIH StrokeNet network will also be uniquely poised to collaborate with other US and international consortia necessary to conduct larger, definitive trials of promising interventions for stroke treatment, prevention, and recovery.

NINDS intends that all multi-center clinical trials in stroke treatment, recovery, or prevention supported by NINDS will be conducted in the NIH StrokeNet and that only in exceptional circumstances will NINDS consider funding multi-site stroke clinical trials outside of this program. Applicants do not need to be part of the existing NIH StrokeNet infrastructure to apply under this FOA.

Key Dates

Posted Date

May 10, 2017

Open Date (Earliest Submission Date)

June 11, 2017

Letter of Intent Due Date(s)

Not Applicable

Application Due Date(s)

July 11, 2017 and then [Standard dates](#) apply 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

[Standard dates](#) apply

Advisory Council Review

[Standard dates](#) apply

Earliest Start Date

[Standard dates](#) apply

Expiration Date

January 8, 2018

Due Dates for E.O. 12372

Not Applicable

Required Application Instructions

It is critical that applicants follow the Research (R) Instructions in the [SF424 \(R&R\) Application Guide](#), except where instructed to do otherwise (in this FOA or in a Notice from the [NIH Guide for Grants and Contracts](#)). 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.

1. Use the NIH ASSIST system to prepare, submit and track your application online.
2. Use an institutional system-to-system (S2S) solution to prepare and submit your application to Grants.gov and eRA Commons to track your application. Check with your institutional officials regarding availability.
3. [Go to Grants.gov](#) to download an application package to complete the application forms offline or create a Workspace to complete the forms online; submit your application to Grants.gov; and track your application in eRA Commons.

Learn more about the various [submission options](#).

Table of Contents

[Part 1. Overview Information](#)

[Part 2. Full Text of the Announcement](#)

[Section I. Funding Opportunity Description](#)

[Section II. Award Information](#)

[Section III. Eligibility Information](#)

[Section IV. Application and Submission Information](#)

[Section V. Application Review Information](#)

[Section VI. Award Administration Information](#)

[Section VII. Agency Contacts](#)

[Section VIII. Other Information](#)

Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Purpose

To facilitate the cooperation and partnering of public and private funding organizations, universities, academic medical centers, research institutes, contract research organizations, biotechnology companies, and pharmaceutical companies in the advancement of interventions for stroke prevention, treatment, and rehabilitation, NINDS has formed the NIH Stroke Clinical Trials Research Network (NIH StrokeNet, http://www.ninds.nih.gov/research/clinical_research/NINDS_stroke_trials_network.htm). The NIH StrokeNet comprises a National Clinical Coordinating Center (NCC), a National Data Management Center (NDMC) and 25 geographically distributed Regional Coordinating Centers (RCC) with over 350 affiliated stroke centers.

The NIH StrokeNet network will consider the breadth of cerebrovascular disease, beginning with patients identified with an acute stroke through stroke rehabilitation and primary and secondary stroke prevention for pediatric and adult patients.

The network will provide a robust, standardized, and accessible infrastructure to facilitate rapid development and implementation of NINDS-funded stroke trials. The network is designed to increase the efficiency of stroke clinical trials by facilitating patient recruitment and retention, supporting novel methodologies and streamlined approaches to accelerate the development of promising stroke therapies, and enabling comparison between approaches.

Scope of the Program

NINDS has established NIH StrokeNet to facilitate and streamline the execution of clinical trials in stroke. Thus, it is expected that all multi-center clinical trials for stroke treatment, prevention, and recovery supported by NINDS will be considered for implementation through NIH StrokeNet.

This FOA encourages and provides a mechanism for the submission of applications for multi-center exploratory and confirmatory clinical trials focused on promising interventions, including pragmatic trials performed in large numbers of patients with minimal alteration from clinical practice and low per-patient costs. Also eligible are biomarker- and outcomes-validation studies that are immediately preparatory to trials in stroke prevention, treatment, or recovery. Exploratory clinical trials must include a clearly defined go/no-go pathway toward advancement to a future Phase 3 trial. In addition, the network will support studies to validate biomarkers with demonstrated promise to inform Phase 2 clinical trials. It is NINDS' intention that NIH StrokeNet will maintain a balanced portfolio of studies in each of these three areas, defined as follows:

- **Primary and secondary prevention stroke trials** – studies of agents, devices, or strategies to prevent recurrent stroke in survivors of stroke or transient ischemic attack (TIA), or to prevent first stroke in high-risk populations.
- **Emergent management or acute stroke treatment trials** – studies of agents, devices, or strategies to intervene during the acute phase of stroke with the goal of reducing brain injury and promoting optimal patient recovery; may include pre-hospital as well as emergency department or in-patient approaches; includes all stroke types.
- **Neuro-recovery and rehabilitation stroke trials** – studies of agents, devices, or strategies to improve long-

term recovery, including cognitive, behavioral and/or motor function or quality of life outcomes, and/or to reduce the time to optimal recovery in patients after the acute period.

The use of innovative and efficient study designs is encouraged, such as adaptive dose-finding designs, designs incorporating plans for sample size recalculation, and futility designs. Applications for exploratory studies (for example, early dose ranging studies with biomarker outcome, early proof of mechanism or proof of concept trials) are encouraged when appropriate. For medical devices, Early Feasibility and Traditional Feasibility study designs may include single-arm case series, on-off interventions (patients as own controls), device-device comparisons, comparisons to historic controls, comparisons to performance controls, or adaptive/Bayesian designs.

Priority of proposed network trials deemed by peer review to be highly meritorious will be based on factors including infrastructure capacity and availability of patient populations considering current ongoing trials within the network. Applicants may submit a proposed study at any time but timing of funding and initiation of the study will be determined by the NINDS with input from the NIH StrokeNet leadership as necessary to assure that studies can be conducted within the proposed timeline included in the research plan of the application.

While additional sites outside of the NIH StrokeNet network of Regional Coordinating Centers may be required, NINDS expects that any confirmatory (Phase 3) trial conducted within the network will utilize most or all of the Regional Coordinating Centers. Exploratory trials and biomarker validation studies are expected to use at least 5 Regional Coordinating Centers and should be feasible within the network with the addition of relatively few non-NIH StrokeNet sites (note that the applicant institution, if not a NIH StrokeNet site, may be included as a performance site in the study). The final number of sites needed for a proposed study will be determined following a feasibility assessment by the NIH StrokeNet.

Exploratory Trials

Examples of appropriate exploratory studies under this FOA include, but are not limited to, multi-center studies designed for the following purposes:

- To evaluate and optimize the dose, formulation, safety, tolerability or pharmacokinetics of an intervention in the target population.
- To evaluate whether an intervention produces sufficient evidence of short-term activity (e.g., biomarker activity, pharmacodynamic response, target engagement, dose-response trends) in a human “proof of concept” trial.
- To select or rank the best of two or more potential interventions or dosing regimens to be evaluated in a subsequent trial, based on tolerability, safety data, biological activity, or preliminary clinical efficacy (e.g., futility trials).
- To evaluate biological activity relative to clinical endpoints.
- For medical devices, in addition to providing initial clinical safety data, appropriate studies are those that inform the next phase of development, usually by finalizing the device design, establishing operator technique, and/or finalizing the choice of study endpoints for the design of a pivotal clinical trial.

Confirmatory (Phase 3) Trials

Confirmatory trials are conducted to provide a definitive answer regarding the safety and efficacy of an intervention or to compare the effectiveness of two or more interventions. The proposed research must address a scientifically important question, provide valuable information to the existing knowledge base, and have public health relevance. The trial design should ensure that high quality, complete data regarding the primary outcome will be collected in the most efficient manner in terms of time, resources, and burden to subjects. Secondary outcomes should be included only when they are anticipated to provide important supportive or explanatory data. The necessity of each secondary endpoint must be justified in light of cost and burden. Pragmatic trials requiring minimal data collection and low cost per subject are encouraged.

This FOA also may be used for the submission of an adaptive trial utilizing a seamless Phase 2/3 transition where data from subjects in Phase 2 are included in the analysis of Phase 3.

Biomarker and Clinical Endpoint Studies

Biomarkers, especially neuroimaging markers of vascular pathology, brain ischemia, or recovery after injury, have been developed for stroke research. The potential applications of biomarkers include guiding early neuroprotective and reperfusion interventions, monitoring neuroplasticity in stroke recovery, and expediting therapy development. Some biomarkers have been validated in multi-center studies, but their full potential to advance research awaits standardization and adoption across a clinical trials network. Similarly, for certain stroke trials the “road block” to evaluating a therapeutic approach may be the lack of a valid clinical endpoint.

This FOA encourages the submission of studies to validate biomarkers or clinical outcomes with demonstrated promise to inform Phase 2 clinical trials. Depending on the scientific questions posed, biomarker studies supported under this program might be stand-alone protocols or could be embedded within a network stroke trial. Studies designed for biomarker discovery are not suitable for this FOA.

Implementation

Applicants should make note of the following:

(1) Working with NIH StrokeNet is a cooperative venture between NINDS, the NIH StrokeNet and the applicant. Potential applicants will be provided guidance by NINDS Program Staff and the NIH StrokeNet Executive and Steering Committees. Potential applicants are strongly encouraged to contact NINDS Scientific/Research Contacts (see Section VII. Agency Contacts) in order to discuss the appropriateness of the proposed study to be conducted within the NIH StrokeNet. Prior to submission of the grant, applicants will be encouraged to work closely with the NIH StrokeNet Investigators in developing their research plan, assessing the feasibility of the study, and developing an appropriate budget to conduct the research. The additional interaction with the network is intended to harness the scientific clinical trial expertise in the network and to establish early collaborations necessary for successful conduct of the research plan. Potential applicants are strongly encouraged to start the process early and allow ample time (i.e., 4-6 months) to prepare and submit a competitive NIH StrokeNet project application.

(2) Applicants to this FOA will be required to incorporate the NIH StrokeNet infrastructure (http://www.ninds.nih.gov/research/clinical_research/NINDS_stroke_trials_network.htm) into their proposed study, including central coordination through the NCC, data management through the NDMC, and subject recruitment and trial implementation at the RCCs and affiliated sites. It is not required that all sites participate in every trial. Additional (ad hoc) performance sites that are not currently NIH StrokeNet sites may be proposed to fulfill specific study requirements. All applicants and ad-hoc non-NIH StrokeNet sites will be required to use the master clinical trial agreements and central IRB that have been established for NIH StrokeNet.

(3) Following peer review, the operational clinical protocol for trials selected for funding will be finalized by the NIH StrokeNet protocol working group and are expected to incorporate recommendations that may come from the peer review process. The NIH StrokeNet team was established by NINDS based on peer- and Council review to form a group of outstanding clinical trial experts from the fields of neurology and statistics with a proven record of developing high quality protocols. Final protocols will be reviewed and approved by NINDS prior to funding the application.

(4) This FOA is intended to support studies in patients, not healthy volunteers. Applications to conduct exploratory trials in healthy volunteers should be submitted to a separate announcement, PAR-17-122 (<https://grants.nih.gov/grants/guide/pa-files/PAR-17-122.html>). All trials proposing use of an investigational agent or device must have an active IND or IDE or documentation of exemption at the time of submission of the application (see <https://grants.nih.gov/grants/guide/notice-files/NOT-NS-11-018.html>).

(5) Device trials: The NIH recognizes that devices can vary greatly in terms of basic form and function, physiological bases for therapy, degree of invasiveness, etc. Consequently, the appropriate pathway to market may require a traditional Feasibility and Pivotal study in support of an eventual Pre-Market Approval submission, or may require a more limited study to address specific issues in support of an FDA 510(k) or 510(k) De Novo submission. Clinical studies involving devices may utilize the entire NIH StrokeNet network, or a more limited subset of centers selected based on appropriate expertise for the given device. Investigators are encouraged to contact the NINDS Scientific/Research Contact as early as possible to discuss how the NIH StrokeNet network may best be utilized in support of their specific device project. NINDS anticipates that the majority of device projects utilizing NIH StrokeNet will be traditional Feasibility Studies in order to optimally leverage network advantages. An Early Feasibility Study should be designed [in accordance with FDA's draft guidance, "Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies", see <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277670.htm>] to allow for early clinical evaluation of devices to provide proof of principle and initial clinical safety data while device design and operations are still in development. A Traditional Feasibility Study is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan a Pivotal Study.

(6) Rationale: Exploratory and confirmatory clinical trials proposed for this network must anchor their rationale in (1) an unmet medical need; (2) a plausible biological mechanism; (3) rigorous preclinical (in vitro and/or in vivo) data; and/or (4) early clinical data. The individual weight given to each of these 4 criteria should be carefully assessed in the context of the specific application; there is no requirement to provide support from all four areas. The major findings of the studies, whether preclinical or clinical, that led to the proposed clinical trial should provide a compelling rationale that the proposed intervention will be effective. Data from preclinical and pilot studies demonstrating the need for and the feasibility of the trial should be presented when available. While the NINDS recognizes that animal models for stroke prevention, treatment, and recovery may be of limited informative value, the applicant should specifically address the rigor of any animal studies being used as support (<https://grants.nih.gov/grants/guide/notice-files/NOT-NS-11-023.html>). Preclinical data (such as from animal studies) that do not sufficiently meet the rigor guidelines or are not sufficiently associated with the human condition may be inadequate to support the rationale for the study.

(7) Pharmacometrics: Applications seeking to obtain data needed for pharmacometric modeling are permitted, with the ultimate aim of enabling the optimal design of a future efficacy trial of an intervention.

(8) The award and continuation of funding are subject to milestones to be specified in the notice of grant award according to NINDS policies.

(9) NIH Resources: As appropriate, applicants are strongly encouraged to make use of the following resources for clinical research including:

- Clinical and Translational Science Award (CTSA) program (<https://www.ctsacentral.org/>);
- NeuroQOL (<http://www.neuroqol.org/>);
- NIH Toolbox (<http://www.nihtoolbox.org/>);
- PROMIS (<http://www.nihpromis.org/>); and
- NINDS Common Data Elements (<http://www.commondataelements.ninds.nih.gov/>).

(10) Mobile Technologies: Applicants are strongly encouraged to consider utilizing (at least experimentally) mobile technologies to facilitate data collection and protocol adherence on the part of research participants and study site staff.

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
Renewal
Resubmission
Revision

The [OER Glossary](#) and the SF424 (R&R) Application Guide provide details on these application types.

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

The maximum requested project period cannot exceed 5 years but the actual funded project period is dependent on reaching specific milestones as described in this FOA.

NIH grants policies as described in the [NIH Grants Policy Statement](#) will apply to the applications submitted and awards made in response to 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](#), **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](#) 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 \(DUNS\)](#) - 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 \(SAM\)](#) (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](#) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- [eRA Commons](#) - 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.

It is not necessary that the designated study PD(s)/PI(s) be part of the NIH StrokeNet infrastructure in order to be eligible to apply to this FOA.

2. Cost Sharing

This FOA does not require cost sharing as defined in the [NIH Grants Policy Statement](#).

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](#)).

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 Research (R) Instructions in the [SF424 \(R&R\) Application Guide](#), including [Supplemental Grant Application Instructions](#) 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](#).

Page Limitations

All page limitations described in the SF424 Application Guide and the [Table of Page Limits](#) 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.

Facilities and Other Resources: A specific statement should be included regarding how Clinical and Translational Science award (CTSA) program (<https://ctsacentral.org>) resources will be leveraged, if applicable. Describe what CTSA services will be used at each participating CTSA site and how the use of the CTSA impacts the trial budget.

Other Attachments: The following documents are to be included in the application in the order listed below

1. *Clinical Protocol*. A full clinical protocol of the proposed study should be included. At the time of this writing, the FDA and NIH had developed a draft Clinical Trial Protocol Template for Phase 2 and 3 IND/IDE Studies (<http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials>), which should be modifiable to any type of clinical trial.
2. *Statistical Analysis Plan (SAP)*. This document should provide details on the analyses described in the protocol, including a detailed description of how the statistical analysis of the primary, secondary and other endpoints will be performed, how the sample size was determined, how missing data will be handled, plans for interim analyses for safety, efficacy and futility, plans for recalculation of the sample size midway through the trial (if applicable), etc. If computer simulations were used to investigate the operating characteristics of complex clinical trial designs (such as adaptive designs), to choose between alternative outcome measures, or to determine sample size, by taking into account the impact of noncompliance, missing data, subject eligibility criteria, etc., sufficient details about the simulations should be provided if the SAP. See the article, "The design of simulation studies in medical statistics", by Burton et al., *Statist. Med.* 2006: 25-4279-4292 for guidance on how to document a simulation study. It is particularly important to discuss the range of conditions that were considered in the simulation and why this range was considered appropriate, how robust the findings were across the range of conditions considered, and how the study will adjust for any design deficiencies (e.g., bias, loss of power) the simulations revealed.
3. *Informed consent forms (ICFs) and, if applicable, assent form(s)*. The applicant should consider including language in the ICF to allow broad data and specimen access for subsequent research in order to maximize the value of subject samples and data and accelerate progress beyond the trial itself. (See http://www.ninds.nih.gov/research/clinical_research/toolkit/model_informed_consent.pdf for suggested ICF

language).

4. *Documentation of availability of eligible **subjects*** at clinical sites, presented in tabular format and a supporting letter from NIH StrokeNet indicating their ability and capacity to collaborate and conduct the proposed study.

5. *Documentation of availability of interventional agent(s) or device(s)* as well as plans and support for acquisition and distribution of interventional agent(s) or device(s).

6. *Regulatory Approvals.* If the intervention is a drug, biologic, or device, applicants must provide documentation from the FDA providing information on one of the following scenarios:

(a) The protocol has been submitted under an open IND and the IND is not under full or partial hold. Under this scenario, applicants must provide documentation such as a "may proceed" email or letter from the FDA.

(b) The protocol has been submitted as an original IDE or as a new study under an open IDE, and FDA has fully approved the IDE or IDE supplement. Under this scenario, applicants must provide documentation of an IDE or IDE supplement full approval letter from the FDA.

(c) The protocol has been submitted under an IND and is on full or partial hold. Under this scenario applicants must provide full documentation from the FDA on the reasons for hold and the FDA recommendations. Applicants should discuss how they intend to address the hold issues and when they believe they will have FDA approval to proceed with trial implementation.

(d) The protocol has been submitted as an original IDE or as a new study under an open IDE, and FDA has conditionally approved the IDE or IDE supplement. Under this scenario applicants must provide full documentation from the FDA on the conditions of approval. Applicants should discuss how they intend to address these conditions and when they believe they will have FDA approval to proceed with trial implementation.

(e) The protocol is exempt from an IND. Under this scenario applicants must provide a copy of the exemption email or letter from the FDA.

(f) The protocol is either exempt from the IDE regulations or does not require IDE approval because it is determined to be nonsignificant risk. Under this scenario applicants must provide either an IDE exemption letter or a copy of the risk determination letter from the FDA.

Applications that do not include this information will be withdrawn and not reviewed. Prior to grant award, awardees who do not have an exemption from the FDA must provide any additional FDA correspondence regarding the status of the protocol to the NINDS, especially if the trial has been placed under full or partial hold.

7. *Milestone Plan.* Applications must include proposed yearly go/no-go milestones. While final milestones will be determined at the time of grant award, the applicant should propose clear milestones that provide objective, quantitative outcomes that will justify continuing the project. Milestones are not equivalent to aims but rather are determinants of whether a study continues or stops. The proposed milestones must include achievable goals for the start-up stage, feasibility stage, and completion stage of the project as follows:

- Completion of start-up activities (finalization of protocol, contracting of sites, registration in ClinicalTrials.gov, completion of any final regulatory approvals, etc.)
- Enrollment of the first subject
- Enrollment of 25%, 50%, 75% and 100% of the projected recruitment for all study subjects, including women, minorities and children (as appropriate)
- Expected timing of proposed interim analyses and, for adaptive designs, implementation of pre-specified adaptation plan
- Completion of data collection time period
- Completion of primary endpoint and secondary endpoint data analyses

Completion of final study report

- Publication of primary study results
- Reporting of results in ClinicalTrials.gov
- Submission of final public use dataset to NINDS

Proposed milestones should be included for the entire trial, including any anticipated time beyond the five-year award. This information will be used for planning purposes and to support the rationale for the full trial but does not guarantee continued funding beyond the initial funding cycle.

SF424(R&R) Senior/Key Person Profile

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

R&R or Modular Budget

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

The budget for all clinical projects proposed to be conducted within NIH StrokeNet should be largely planned on a fee-for-service basis with detailed per-patient costs. That budget may include clinical trial costs such as:

- Up to 4 person-months for the protocol PD(s)/PI(s) (even if that person is also an NIH StrokeNet RCC PD(s)/PI(s).
- Support for a study-specific clinical coordinator at the applicant's site.
- Study-related procedures/materials.
- Clinical site operations for any proposed non-NIH StrokeNet ad-hoc sites.
- Subject monitoring costs and protocol-specific costs required for NCC or NDMC operations not otherwise covered by the NCC and NDMC awards. Applicants are encouraged to work with the NCC and NDMC staff to determine protocol-specific costs to be included in the budget.
- All NIH StrokeNet projects will utilize the NDMC for data management and reporting activities. Applicants are encouraged to include a statistician to provide study-specific leadership in statistical design and analysis; however, applicants who do not have access to a statistician may propose to make use of statistical expertise at the NDMC.

The budget will not include costs that are already covered by the NINDS infrastructure:

- NIH StrokeNet RCC PD(s)/PI(s) effort, other than the protocol PD(s)/PI(s)
- NIH StrokeNet RCC coordinator time.

For a seamless Phase 2/3 trial, the budget must include costs adequate to complete both phases of the adaptive design.

NINDS expects that the total cost for the proposed project (direct cost plus F&A) will not exceed \$25,000 per subject randomized into the trial. Budgets exceeding this guideline should be adequately justified in the application. The NINDS strongly encourages applicants to consider simple and/or pragmatic trial designs that minimize per-subject data collection and cost.

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:

Specific Aims: Applicants should describe the potential impact of the proposed research. The hypotheses and

specific aims of the trial must be clearly and concisely stated. The primary and secondary outcomes to be measured must be defined. The inclusion of secondary aims should be justified by describing the importance of the supportive or explanatory data.

Research Strategy:

Significance and Biological Relevance: Applicants must state concisely the need, rationale, timeliness, and scientific relevance of the proposed study. It is particularly important that there be a discussion of how the trial will test the hypothesis proposed and how results of the trial (positive or negative) may be explained based on the biological action of the proposed intervention. The application must present an overview of the state of the science, current status of therapeutics for the disease, and relevance of the trial for stroke prevention, treatment, or recovery. The applicant should also identify other (industry or academic) current or planned trials that potentially overlap with the proposed study. The timeliness of the proposed study should be discussed in the application.

Potential Impact of the trial: Applicants should also include a description of the potential impact of the proposed research on clinical care - regardless of the results - and estimate the public health impact relative to the number of afflicted individuals in the U.S. and/or global population annually.

Prior Studies and Rationale for Development: Applicants should describe the full body of evidence being used to support the proposed study and comment on the justification for moving forward with this proposed clinical study. Proposed clinical trials must anchor their rationale in (1) an unmet medical need; (2) a plausible biological mechanism, as well as (3) preclinical (in vitro and/or in vivo) data and/or (4) early clinical data. Their individual weight should be carefully assessed in the specific context of the application at hand; the applicant is not required to provide support from all four areas. The major findings of the studies, whether preclinical or clinical, that led to the proposed clinical trial should provide a compelling rationale for the belief that the proposed intervention may be effective. Data from preclinical and pilot studies demonstrating the need for and the feasibility of the trial should be presented when available. While the NINDS recognizes that animal models for stroke prevention, treatment, and recovery may be of limited informative value, the applicant should specifically address the rigor of any animal studies being used as support (<https://grants.nih.gov/grants/guide/notice-files/NOT-NS-11-023.html>). Applications for drugs or biologics should provide compelling scientific evidence that the investigational agent and dose proposed for study will reach/act upon the designated target or that its mechanism of action is such that it is expected to be of benefit in ameliorating a specific aspect of the disease.

Approach: Applicants should provide a concise summary of the protocol including the following items below. Specific details can be referenced to the attached full protocol. NINDS expects that the full protocol included in the application should support this concise summary.

Include a brief summary of the following:

- A description and rationale for the selected trial design.
- A description of the study population and why it is an appropriate group to answer the question under study.
- A description and rationale for selection of the study outcomes and endpoints.
- A list of subject inclusion/exclusion criteria, or of group eligibility criteria for group-randomized trials.
- Subject recruitment and retention plans, including a discussion of the ability of sites to recruit and retain the proposed number of subjects, including women and minorities. Data supporting recruitment and retention estimates must be provided as an "Other Attachment". Evidence should be provided that relevant stakeholders (e.g. potential subjects, referring and treating physicians, patient groups) have equipoise, view the question to be important and consider the study acceptable.
- For confirmatory (Phase 3) trials, a discussion of the evidence regarding whether clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected.
- Applicants must include a plan to enroll women and minorities. Considerations that may contribute to successful inclusion are appropriate site selection, patient- or community-engagement for the major elements

of the project, use of focus groups to address barriers to inclusion, etc. Applicants should also include a discussion of how the gender and minority findings will be reported to the NINDS. For exploratory trial applications, investigators should consider including a section that addresses how the results in women and minorities will inform the design of the next steps.

- A description of the intervention to be tested and how it will be administered.
- A description of all assessments including clinical, laboratory, physiological, behavioral, patient-centered, or other outcomes addressing the primary and secondary research questions. Use of patient reported outcomes, including those available through PROMIS and NeuroQoL, as well as non-traditional data collection approaches (e.g., telephone, mobile devices or web-based systems) should be considered.
- A discussion regarding how the following resources for clinical research will be utilized, as applicable:
 - NeuroQOL (<http://neuroqol.org>);
 - NIH Toolbox (<http://www.nihtoolbox.org>);
 - PROMIS (<http://nihpromis.org>); and
 - NINDS Common Data Elements (<http://www.commondataelements.ninds.nih.gov>)
- A discussion of potential biases and/or challenges in the protocol and how they will be addressed.
- A discussion of how the study investigators will be kept blinded to treatment group-specific data during the course of the clinical trial. Applicants should describe how study statistical personnel will interact with the NDMC, who will be the blinded and un-blinded statisticians, etc.

For an exploratory trial of a drug, device or biologic, specific plans for the next steps of the therapy's development (such as a future efficacy trial) and proposed go/no-go criteria must be succinctly stated. For applications proposing to conduct a seamless Phase 2/3 trial, where data from subjects in Phase 2 are included in the analysis of Phase 3, a transition plan from the Phase 2 component to the Phase 3 component should be described and trial termination plans should be defined in the event that the results of Phase 2 do not support continuation to Phase 3.

Protection of Human Subjects: Assurance of the protection of human participants and the biohazard safety of employees (if applicable) must be provided for the overall study and for each clinical site. The applicant must discuss any issues which might lead to concern for the welfare of participants. Additionally, the human subjects section of the application must address data security measures and confidentiality.

Letters of Support: If there will be subcontracts or service agreements for personnel or facilities, include documentation of such commitments, co-signed by a business official and the investigator at the participating center.

If there are agreements with collaborating industry partners, include documentation of the agreements, co-signed by a business official and an appropriate official at the company.

If CTSA resources will be utilized, include letter of support from each site CTSA program officer concurring with the specific plan for using these resources.

If some trial costs are to be borne by sources other than NIH, include documentation of this support, signed by individuals who have the authority to make a commitment on behalf of the organization they represent.

Applicants are encouraged to include letters from patient organizations or other supporting documentation to show that patients were included as partners in the concept development and design of the trial.

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, with the following modification:

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan in accordance with the NIH StrokeNet data sharing policies.
- Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genomic Data Sharing Policy) are expected when applicable.

- The National Institutes of Health (NIH) Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by the NIH, will ensure that their NIH-funded clinical trials are registered at, and that summary results information is submitted to, ClinicalTrials.gov for public posting (see NOT-OD-16-149 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html>). The purpose of the policy is to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTrials.gov. Applicants must submit a plan for the dissemination of NIH-funded clinical trial information that will address how the expectations of this policy will be met.

Appendix:

Do not use the Appendix to circumvent page limits. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

PHS Inclusion Enrollment Report

When conducting clinical research, follow all instructions for completing PHS Inclusion Enrollment Report as described in the SF424 (R&R) Application Guide.

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](#), 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](#), the application deadline is automatically extended to the next business day.

Organizations must submit applications to [Grants.gov](#) (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](#), 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](#).

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](#).

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

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](#) 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](#).

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the [NIH mission](#), all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

For this particular announcement, note the following:

1. Approved projects will be implemented through the NIH StrokeNet infrastructure and will make use of previously approved sites, resources, and investigators at the NIH StrokeNet National Coordinating Center, National Data Management Center, and Regional Coordinating Centers and their satellite stroke centers. Timing of a grant award and initiation of projects approved by peer review and Council will be determined by the NINDS with input from the NIH StrokeNet leadership as necessary in order to assure that studies can be conducted within the proposed timeline included in the research plan of the application. Prioritization of trials to be conducted in the network will be determined based on factors including infrastructure capacity as well as availability of patient populations considering current ongoing trials within the network.
2. Participant Enrollment: NIH StrokeNet includes a strong, flexible consortium of sites with capacity to implement trials. Trial enrollment will be overseen by the consortium.
3. Environment: The NIH StrokeNet infrastructure (NCC, NDMC and RCCs) was selected following peer review to provide an optimal environment and mechanism for conducting relevant projects, including centralized clinical trial management, data management, and oversight of activities at clinical centers.
4. Investigators: For NIH StrokeNet projects, the PD(s)/PI(s) will work closely with the NIH StrokeNet investigators, who have been selected for their experience and training in stroke clinical research. While some applicants will be relatively junior in their careers, NIH StrokeNet provides a cadre of experienced clinical trial experts who can ensure high quality implementation and oversight of studies. The PD(s)/PI(s) therefore do not need to bring as much clinical research experience as they would have to bring to a non-NIH StrokeNet project.
5. Applications will be evaluated for the scientific rationale/premise and clinical need of the study. Proposed clinical trials must anchor their rationale in (1) an unmet medical need; (2) a plausible biological mechanism; (3) preclinical (in vitro and/or in vivo) data; and/or (4) early clinical data. Their individual weight should be carefully assessed in the specific context of the application at hand; the applicant is not required to provide support from all four areas. Assessment of the overall impact will include the evaluation of the experimental design and all of the review criteria described below.

Overall Impact

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

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

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

How adequate and scientifically rigorous is the body of preclinical or clinical research supporting the study rationale? How compelling is the justification for the development of the proposed intervention in terms of potential advances in clinical practice, public health, and/or patient quality of life? How convincing is the evidence that equipoise exists in the medical and patient communities and the intervention is ready for clinical development?

What is the potential of the trial to advance the field as related to clinical practice, public health, unmet medical need, and/or patient quality of life even if (a) the proposed study design, methods, and intervention are not innovative, or (b) the results of the trial are negative? How would the intervention or treatment approach affect management and care of stroke patients? How would the project advance the field regardless of its outcome?

For exploratory trials, biomarker studies, or clinical endpoint studies, evaluate whether the proposed project is likely to yield the answers needed to proceed to the next step in developing the intervention. Is it clear why the proposed study is essential to inform the design and implementation of a subsequent efficacy trial, or enable a “go/no-go” decision regarding further clinical development of the intervention?

For confirmatory trials, assess whether there is a sufficient body of preclinical and/or clinical research of high scientific rigor to support the study rationale and whether the intervention is ready for Phase 3 evaluation. Is the proposed intervention justified in terms of potential advances in clinical practice, public health, and/or patient quality of life? Is there evidence of equipoise in the medical and patient communities? Are there any ethical concerns?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or 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? Evaluate whether the PDs)/PI(s) of the project is/are well-positioned to provide scientific leadership to the proposed study while collaborating with the NIH StrokeNet NCC, NDMC, and RCC investigators.

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? Assess the extent to which the proposed study has the potential to advance the field (e.g., by evaluating a new target mechanism, or by advancing the validation of a biological or clinical outcome) even if (a) the proposed study design, methods, and intervention are not innovative, and/or (b) the results of the trial indicate that further clinical development of the intervention is unwarranted.

Approach

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

How appropriate are the primary and secondary outcome measures? How appropriate are the eligibility criteria, randomization plan (if applicable), methods of blinding, sample size, study power, data management plans, and plans for training of site personnel?

How appropriate is the proposed plan for inclusion or exclusion of sex/gender and racial/ethnic groups for the scientific objectives of the trial? How appropriate are the plans for subject outreach, recruitment, retention and follow-up?

How appropriate are the milestones? How likely is the trial to be completed within the project period?

How adequate are the study documents (e.g., protocol, consent, investigator's brochure) to allowing the implementation of a high quality study? Do the study documents comply with Good Clinical Practice (GCP)?

How well does the project leverage the use of existing NIH tools, NINDS networks, and/or other resources?

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

Environment

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

While the NIH StrokeNet environment has already undergone peer review and is fully established, the following issues should be considered with respect to each application: Have the sites provided adequate or reasonable estimates of the number of patients that they expect to be able to enroll? Does this project include a partnership with the private sector (e.g. patient groups and/or industry), and if so, have agreements with proposed partners been established? Have any foreign organizations involved in the proposed study documented the compatibility of their data collection methods with U.S. data collection methods? Is there evidence that the study drug or device will be available in sufficient quantities to ensure feasibility of the project? Are substantive letters of support or other documentation provided to assure commitment of subcontractors, consultants, and/or service agreements for personnel and facilities?

Additional Review Criteria

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

Protections for Human Subjects

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

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the [Guidelines for the Review of Human Subjects](#).

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the [Guidelines for the Review of Inclusion in Clinical Research](#).

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](#).

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

For Renewals, the committee will consider the progress made in the last funding period.

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](#); (2) [Sharing Model Organisms](#); and (3) [Genomic Data Sharing Plan \(GDS\)](#).

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 NINDS, in accordance with [NIH peer review policy and procedures](#), 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 submitted in response to this FOA. 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](#). 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](#).

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](#).

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](#) 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](#) 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](#) and [Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities](#). More information is provided at [Award Conditions and Information for NIH Grants](#).

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.

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>; and <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>. 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> 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>.

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.

Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS grant administration regulations at 45 CFR Part 75 (, and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the 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 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:

- 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 between investigators, advisory and steering committees, and NINDS representatives.
- Interacting with the NIH StrokeNet National Coordinating Center and the NIH StrokeNet National Data Management Center as well as NIH StrokeNet Regional Coordinating Centers and any ad-hoc sites.
- Acquiring an IND or IDE from the FDA if an investigational agent or device is to be used.
- Acting as a member of the NIH StrokeNet Steering Committee for the duration of the study with possible participation in steering groups for planning, quality control, capitation, publications etc.
- 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.

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

NINDS staff involvement will include oversight of the IRB-approved protocol by the NINDS Program Official, documentation of adequate serious adverse event management and reporting, and regular communications with the Principal Investigator and staff; additional involvement generally includes participation in meetings of the steering committee and other leadership committees. Specifically:

- An NINDS Project Scientist working with the Principal Investigator and network investigators 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 NINDS retains the option to obtain periodic external peer review of progress.
- The NINDS Project Scientist will function as one of several co-investigators, collaborating and interacting as necessary with the Principal Investigators in accomplishing the overall goals of the Research Program.
- In addition, an NINDS Program Official will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice.
- A separate NINDS Program Official, from the Office of Clinical Research, will serve as the NINDS liaison to the Data and Safety Monitoring Board (DSMB).
- If the proposed trial should require that FDA issue an IND/IDE, the NINDS Project Scientist and/or Program Official(s) will be present at any meetings held with the FDA related to this NIH-funded protocol.

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 NINDS will consider ending support and negotiating a phase-out of the award. The NINDS retains the option to obtain periodic external peer review of progress. Milestones will be established by the NINDS prior to the award of the grant based on recommendations from the primary review group. NINDS will make an award for 2 to 3 years in order to start-up the trial and establish performance feasibility. Continuation of the award past this feasibility period will be contingent upon a demonstrated ability to meet milestones indicating that the trial can be implemented as planned. Feasibility milestones will be defined at the start of each trial and will be monitored closely by the Institute-appointed DSMB and NINDS Program Official. Achievement of these milestones will be evaluated by NINDS 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:

None; all responsibilities are divided between awardees and NIH staff as described above.

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 individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulations 42 CFR Part 50, Subpart D and HHS regulations 45 CFR Part 16

3. Reporting

When multiple years are involved, awardees will be required to submit the [Research Performance Progress Report \(RPPR\)](#) annually and financial statements as required in the [NIH Grants Policy Statement](#).

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](#).

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 on all subawards over \$25,000. See the [NIH Grants Policy Statement](#) 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 registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)

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

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

[Grants.gov Customer Support](#) (Questions regarding Grants.gov registration and submission, downloading forms and application packages)

Contact Center Telephone: 800-518-4726

Email: support@grants.gov

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)

Email: GrantsInfo@nih.gov (preferred method of contact)

Telephone: 301-945-7573

Scientific/Research Contact(s)

Claudia Scala Moy, PhD

National Institute of Neurological Disorders & Stroke (NINDS)

Telephone: 301-496-9135

Email: moyc@ninds.nih.gov

Peer Review Contact(s)

Chief, Scientific Review Branch

National Institute of Neurological Disorders and Stroke (NINDS)

Telephone: 301-496-9223

Email: nindsreview.nih.gov@mail.nih.gov

Financial/Grants Management Contact(s)

Tijuanna E. DeCoster, Ph.D., MPA

National Institute of Neurological Disorders & Stroke (NINDS)

Telephone: 301- 496-9231

Email: decostert@mail.nih.gov

Section VIII. Other Information

Recently issued trans-NIH [policy notices](#) may affect your application submission. A full list of policy notices published by NIH is provided in the [NIH Guide for Grants and Contracts](#). All awards are subject to the terms and conditions, cost principles, and other considerations described in the [NIH Grants Policy Statement](#).

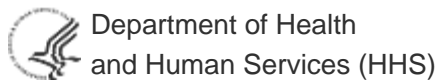
Authority and Regulations

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](#)

[NIH Funding Opportunities and Notices](#)





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