Section 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Institute of Neurological Disorders and Stroke (NINDS)
Research Opportunity Title	**StrokeNet Thrombectomy Platform (STEP) – Domain Clinical trials to be conducted in STEP: Stage 1 Preliminary Application (OT2)**
Activity Code	OT2: Application for an Other Transaction Agreement
Research Opportunity Number	OTA-24-009
Related Notices	
Key Dates:	Posted Date: February 8, 2024
	Open Date (Earliest Submission Date): March 1, 2024
	Application Due Date(s): Rolling Submission
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Content by Sections

Section 2. Objectives of this Opportunity

The purpose of this research opportunity announcement (ROA) is to invite Stage 1 Preliminary Applications for clinical trials that will address the indication expansion of current endovascular therapy (EVT) criteria, concomitant medical therapies added to EVT, novel EVT devices, and(STEP) within the NIH StrokeNet network.

Background:

Stroke is a disabling, often fatal and expensive disorder that is a major public health burden and is the leading cause of adult disability. Globally it is the second leading cause of death, but in North America stroke has fallen to the fourth most common cause of mortality as the result of ongoing successes in prevention and acute care. Vascular disease of the brain can manifest not only as overt stroke but also as silent infarction and diffuse white matter disease with cognitive and functional decline. Stroke is a syndrome, with two broad types (ischemic and hemorrhagic) and with multiple possible underlying causes. Although stroke impacts all age groups (including children and especially neonates), the incidence is strongly linked to aging. Stroke will become increasingly prominent in the next 30 years with the projected rise in the proportion of elderly in the US, and it will impose an even more significant toll on individuals, families, and society.

Recent pivotal interventional trials in patients with ischemic stroke due to large vessel occlusion have shown mechanical thrombectomy to be highly beneficial in certain groups of patients up to 24 hours after last known well. However, many questions remain about the potential for benefit or harm of thrombectomy in specific subgroups of patients or certain ischemic stroke phenotypes. Also of interest are considerations such as pre-hospital care and peri-procedural management strategies.

In 2013, the NINDS established the NIH StrokeNet to conduct clinical trials in a centrally coordinated network that includes 27 regional centers that are linked to over 600 stroke hospitals across the United States. The NIH StrokeNet was designed to rapidly initiate and efficiently implement small and large multi-site exploratory and confirmatory clinical trials in stroke which provides an opportunity to address the potential benefit or harm in expanding and/or enhancing treatment or delivery of thrombectomy in specific subgroups of ischemic stroke patients.

To address this need, NINDS initiated the Stroke Thrombectomy Platform (STEP) platform within the existing NIH StrokeNet to use a novel, efficient study design including adaptive and platform designs. STEP uses an FDA approved master protocol and statistical analysis plan that will enable platform trials that answer the above questions using a seamless rolling approach. The STEP platform will allow trials that further refine patient groups that do or do not benefit from mechanical thrombectomy and using which treatment or management approaches will also open the door to testing neuroprotectant strategies in an efficient, timely, and cost-effective manner.

The scope of the STEP platform will address questions across four domains of endovascular therapy (EVT). Those include trials that will address the indication expansion of current EVT criteria, concomitant medical therapies added to EVT, novel EVT devices, and systems of care for EVT. The STEP-platform will make its trial data (such as clinical research data, neuroimaging, and biomarker data) and biosamples if collected available through public-access data and bio-specimen repositories.

NIH StrokeNet Organization

The NIH StrokeNet Network infrastructure consists of one National Coordinating Center (NCC), one National Data Management Center (NDMC), and 27 Regional Coordinating Centers (RCCs) able to coordinate and conduct stroke clinical trials in a large number of centers across the United States.

The NCC provides scientific and organizational leadership to NIH StrokeNet to achieve both efficiency and excellence in the performance of clinical trials. The NCC coordinates the NIH StrokeNet central IRB, establishes clinical trial agreements with the Clinical Sites for trial performance, develops recruitment plans, coordinates study staff training, tracks enrollment and

oversees quality improvement.

The NDMC provides scientific and organizational leadership to the NIH StrokeNet in all aspects of data management, data quality, statistical design, and statistical analysis.

The RCCs provide scientific leadership and conduct the clinical studies. The RCCs are regional academic medical centers that both enroll patients directly and provide organizational leadership to a network of satellite "spokes", or clinical sites, that also enroll patients. Each RCC and their satellite hospitals have physicians and investigators with expertise in a wide variety of stroke types across multiple specialties (e.g., neurology, neurosurgery, neuroradiology, cardiology, hematology, laboratory science, pharmacology, and others), and have access to clinical populations with stroke. The NIH StrokeNet has the ability to include *ad hoc* hubs/spokes if needed for particular clinical trials.

Scope

The STEP-Platform is designed to test the efficacy and safety of clot retrieval in large vessel ischemic stroke. Studies of concomitant medical therapies (including drugs, small molecules, biologics), novel medical devices, surgical and non- pharmacological interventions and or questions addressing systems of care for EVT management, may be considered.

The STEP-platform is integrated within the NIH StrokeNet clinical trials network and will leverage existing infrastructure from that program. Studies that fall outside of this ROA may be directed to use the NIH StrokeNet funding opportunity (NIH StrokeNet Clinical Trials and Biomarker Studies for Stroke Treatment, Recovery, and Prevention (UG3/UH3 Clinical Trial Optional) or another NIH funding mechanism.

Objectives

The purpose of this research opportunity announcement (ROA) is to invite Stage 1 preliminary applications for submission that would address potential EVT questions meeting the scope of the STEP program. This would include addressing clinical trials of EVT indication expansion, concomitant medical therapies added to EVT, novel EVT devices and questions addressing systems of care to improve access to EVT. STEP applications are reviewed in a two-stage process. Applications submitted to Stage 2 will only be accepted by invitation and involve submission of more detailed information (see Section 5: Application Information and Submission).

The preliminary application will provide an overview of the proposed question to be studied and proposed approach. See Section 5: Application Information Submission for detailed instructions.

Section 3. Potential Award Information

Please note: No funding is provided as a result of a Stage 1 Preliminary Application outcome determination. Funding may only be awarded after Stage 2 Protocol Application, based on favorable review and programmatic priority.

After a successful review of the Stage 1 Preliminary Application and upon receiving an invitation to proceed to Stage 2 (OTA-24-010) the asset holder will work with the NIH StrokeNet NDMC to further develop the clinical trial protocol. At Stage 2 the NIH StrokeNet NDMC becomes the applicant of record for the Stage 2 Protocol Application. NIH funds to conduct the study are

awarded directly to the NDMC (through an Other Transactions Agreement) only after successful completion of both stages of application and review by the National Advisory Neurological Disorders and Stroke (NANDS) Council and approval by the NINDS Director. The NIH StrokeNet NDMC then administers the funds to other StrokeNet research components through sub-agreements as appropriate. The asset owner does not receive OT funds.

It is anticipated that there will be multiple concurrent asset clinical trials funded through OT clinical trial parent application.

Authority:
This Research Opportunity Announcement (ROA) is issued with the goal of adding clinical trials to an existing master protocol and statistical analysis plan (SAP) in order to enable stroke thrombectomy platform trials to answer questions using a seamless rolling approach within the existing NIH StrokeNet infrastructure. No OT funds are provided at the STEP application Stage 1. An application that is successful at Stage 2 will result in the asset being eligible to participate in the NIH StrokeNet Platform Program and in the award of OT funds to the StrokeNet NDMC to administer, pursuant to the OT authority described in section 402(n) of the Public Health Service Act, 42 U. S. C. 282(n).

Section 4. Eligibility

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 asset application. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Organizations:

The following entities are eligible to apply under this ROA:

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 Independent School Districts

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 (https://grants.nih.gov/grants/policy/nihgps/HTML5/section_16/16.2_eligibility.htm?Highlight=Foreign%20Component%27) are allowed.

Section 5. Application Information and Submission

Application Process Overview

For STEP clinical trials conducted within the NIH StrokeNet STEP program, there are two stages of application and review:

Stage 1 Preliminary Application: Academic, industry and other investigators (e.g., the asset holder) will submit a preliminary application under this ROA to have their therapeutic candidate "asset" (e.g. EVT indication expansion, concomitant medical therapies added to EVT, novel EVT devices and questions addressing systems of care for EVT) studied within STEP. This application must include detailed information on the proposed asset, including prior basic, pre-clinical and clinical research completed and rationale as well as brief information on the proposed study population and design. Stage 1 Preliminary Applications are received and reviewed on a rolling basis. The review for this stage includes an independent /objective review by a panel of external experts convened by the NINDS. No funding is provided at Stage 1.

Stage 2 Protocol asset (Clinical Trial Supplement) application: Upon completion of the Stage 1 review process, the applicant may be invited to work with STEP and the NIH StrokeNet NDMC to develop a full clinical protocol (to include budget and timeline) for submission under OTA-24-010, resulting in a Stage 2 Protocol Application. The NIH StrokeNet NDMC will be responsible for submission of the Stage 2 application package and the PI of the NDMC will be the "contact PI". The following will be considered in making funding decisions: 1) Scientific and technical merit of the proposed project as determined

by scientific peer review, 2) Availability of funds, and 3) Relevance of the proposed project to program priorities. Protocols selected following the review will be presented to the NANDS Council for concurrence and a funding decision will be made by the NINDS Director. If funded, the OTA trial funds will be released to the NIH StrokeNet NDMC and study implementation may begin within the STEP program.

STEP Clinical Trial Stage 1 Preliminary Application Information:

The preliminary application will incorporate detailed information on:

- The proposed EVT intervention rationale and population (assuring diversity) and how the therapeutic asset will address the unmet clinical need.
- Justification for the proposed intervention, including the proposed target, mechanism of action, drug pharmacokinetic and pharmacodynamic profile, dose, toxicology and/or device specifications.
- Pre-clinical data on mechanism of action, target engagement, safety, and efficacy including a relevant description of the preclinical findings that include randomization, masking of treatment assignment, sample sizing and power analyses, inclusion/exclusion criteria, replication in multiple laboratories, inclusion of sex and age as biological variables, and use of other relevant co-morbidities that may impact the treatment outcome, such as diabetes, hypertension, etc.
- Relevant clinical data and additionally, data from any existing IND, IDE or Investigator Brochure, etc.
- Description of the proposed study plan to test the proposed EVT intervention.

Submission Information:

Applications to the NIH Stroke-Net Thrombectomy Platform must be submitted via NIH eRA ASSIST. Use this ROA number when submitting the application in NIH eRA Commons. Detailed instructions for submitting OT Applications can be found at ASSIST-Instruction-Guide-for-NIH-Other-Transactions.docx (live.com).

Complete applications must be submitted by the Recipient Business Official/Signing Official. The organization must be registered in eRA Commons with one person designated as the Principal Investigator (PI) and one person designated as the Signing Official (SO). The SO's signature certifies that the applicant has the ability to provide appropriate administrative and scientific oversight of the project and agrees to be fully accountable for the performance of the OT award-supported project or activities resulting from the application.

The application must clearly and fully demonstrate the applicant's capabilities, knowledge, and experience. Full applications must be submitted in text-recognizable PDF (Adobe) format, use 11-point font and be single-spaced.

Upon receipt, applications are evaluated for completeness and compliance with application requirements. Applications that are incomplete will not be reviewed and the applicant will be so notified.

The Cover Page should include (no more than 1 page):

- Number and title of this ROA • Project title
- The Recipient's

- Legal entity name
- Address and contact information
- SAM # and expiration date
- Unique Entity ID# and expiration date
- EIN number

- Principal Investigator(s) first and last name, title, organization, mailing address, email address and phone number (with NIH Commons Account information). If multiple PIs are named, the Contact PI must be clearly identified.
- The name and contact information for the Recipient's Business Official, the person authorized to negotiate and bind the Recipient.

Application Requirements:

Abstract (no more than 1 page)

The project abstract is a succinct and accurate description of the proposed work and should be able to stand on its own (separate from the application). It should be informative to other persons working in the same or related fields and understandable to a scientifically literate reader. Do not include proprietary, confidential information or trade secrets in the abstract. If the application is funded, the project abstract will be entered into an NIH database and made available on the NIH Research Portfolio Online Reporting Tool (RePORT) and will become public information. The attachment is limited to one page.

Specific Aims (no more than 3 pages)

State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the research will have on the research field(s) involved. List succinctly the specific objectives of the research. This attachment is limited to three pages.

Senior/Key Person Profile (no more than 5 pages for each Biosketch)

All Key Personnel who are major contributors to the domain asset clinical trial must provide an NIH Biosketch. Do not include NIH Biosketches for key personnel at the NIH StrokeNet NCC, the NDMC, or at the clinical performance sites unless they have a separate specific role in the proposed study. NIH biosketches must conform to a standardized format (https://grants.nih.gov/grants/forms/biosketch.htm).

Clinical Trials Preliminary Application Project Plan (no more than 12 pages)

The Clinical Trial Preliminary Application should include the following information, as applicable. The application must include all the components listed in this section. If certain components are not applicable, please indicate it clearly.

1. **Scientific Rationale/Background for proposed asset**
   - Provide justification and need for the proposed EVT intervention.
     a. for therapeutic and/or device assets, include the proposed target, mechanism of action, drug pharmacokinetic and pharmacodynamic profile, dose, toxicology and/or device specifications.

b. for systems of care interventions, include rationale and procedures relevant to the approach.

- Include data (if applicable) from any existing investigational new drug (IND), investigational device exemption (IDE), or investigator brochure.
- Provide any known adverse effects/safety concerns; manufacture, scale-up, or availability of the asset (e.g., provide agreements if asset is being provided to the study by an outside source); availability of comparator drug/matching placebo; stability storage, handling and usage information; as applicable.
- Describe how the therapeutic asset will address the unmet clinical need and advance its therapeutic space.

2. **Preliminary data supporting the proposed asset**
   - Describe pre-clinical animal data on mechanism(s) of action, target engagement, safety, and efficacy, as applicable.
     - Data describing the rigor of the preclinical findings must include, but are not limited to randomization, masking of treatment assignment, sample sizing and power analyses, inclusion/exclusion criteria, replication in multiple laboratories, inclusion of sex and age as biological variables, and use of other relevant co-morbidities that may impact the treatment outcome, such as diabetes, hypertension, etc., as implemented in testing through the Stroke Preclinical Assessment Network, SPAN, (see: A multi-laboratory preclinical trial in rodents to assess treatment candidates for acute ischemic stroke - PubMed (nih.gov)
   - Describe data from Clinical studies relevant to the factors described above.
   - Include evidence of target engagement; PK/PD data; and Toxicology/carcinogenicity/teratogenicity data, as applicable.

3. **Description of proposed clinical trial plan**
   - Briefly describe the proposed clinical trial plan being proposed to include in the STEP master protocol to include the following:
     - Clinical trial phase
     - The objectives of the trial
     - Outcome measures if in addition to those included in the master protocol
     - Inclusion and exclusion criteria
     - Controls
     - Therapeutic procedures/administration of intervention
     - Projected sample size and power assumptions

Section 6. Independent, Objective Review Information

The Stage 1 application will undergo an objective, independent review. Independent review is an assessment of scientific or technical merit of applications by individuals with appropriate scientific knowledge and expertise. Conflicts-of-interests of review panel members are appropriately managed during the review process in accordance with standard NIH policies. Independent review provides information essential to ensuring selection of applications that best meet the needs of the program using the criteria delineated below and that application selection is conducted in a fair, objective manner free of prejudices and biases. Reviewers provide individual assessments to NINDS of the likelihood for the proposed intervention or modifications to systems of care to exert a sustained, powerful influence on the treatment and management of stroke patients who may currently be considered candidates for EVT.

The reviewers consider only the review criteria below in their individual assessment of scientific merit. 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, or a proposed Clinical Trial may include study design, methods, or an intervention that are not by themselves innovative but address important questions or unmet needs. Additionally, the results of the clinical trial may indicate that further clinical development of the intervention is unwarranted or that it might lead to new avenues of scientific investigation.

Independent/Objective Review Criteria

1. Significance/Innovation
    a. Does the therapeutic question appropriately address a high, unmet therapeutic need for EVT?
    b. Will the therapeutic intervention and proposed study significantly advance the field of EVT therapy?
    c. If the proposed therapeutic intervention is similar to that proposed in prior work, how does the proposal address potential weaknesses/critical barriers or fill gaps identified in prior work?
    d. Does the asset have a proposed target (if known) with a strong rationale and rigorous supporting data to justify testing the question STEP?
    e. Are there rigorous supporting data for the proposed target (if known) with a strong rationale and rigorous supporting data to justify testing the question STEP? Is the rationale for the selection of the target, the level of agreement in the field regarding the target's role in disease pathogenesis and clinical relevance of the target well explained? Does the supporting data sufficiently address randomization, masking of treatment assignment, sample sizing and power analyses, inclusion/exclusion criteria, replication in multiple laboratories, inclusion of sex and age as biological variables, and use of other relevant co-morbidities that may impact the treatment outcome, such as diabetes, etc.?
    f. If the aims of the study are achieved, how will scientific knowledge or treatment development for the condition under study be advanced?

2. Feasibility/Readiness
    a. Is the asset appropriate for a clinical trial within STEP?
    b. Is the candidate intervention ready for the current phase of clinical trial?
    c. Does the overall conceptual framework for conducting this trial in STEP remain realistic?
    d. Are there any barriers to conducting the trial in STEP?
    e. How is the competitive landscape addressed?
    f. Is the asset clearly scalable for both the proposed clinical trial and eventual clinical use?
    g. Are safety and/or biohazard considerations for use of the asset in humans clearly addressed?
    h. Is there a reasonably rapid timeline for bringing this asset to a clinical trial?
        i. For drugs, how are the scale-up, good manufacturing practices, and needed resources addressed?
        ii. For devices, how are device manufacturing, controls, and safety standards addressed?
        iii. For drugs and devices:
            1. Is manufacturing consistent with relevant standards and safety testing (ISO, IEC, IEEE, etc.)?
            2. Does the regulatory history show that the asset is IND/IDE ready?

iv. For modifications to systems of care:
    1. Is the rationale reasonable?
    2. Can the approach be implemented?

3. Data
    a. How robust are the pre-clinical data in support of the proposed asset provided?
    b. How robust are the clinical data in support of the proposed asset provided?
    c. Does the therapeutic intervention have a proposed target, if known, with a strong rationale and rigorous supporting data to justify testing the question within STEP?
    d. For drugs, how robust is the pharmacokinetic/pharmacodynamic information?
    e. For devices, how sound is the mode of use and supporting data?
    f. For systems to improve access to EVT?
        i. Is the rationale reasonable?
        ii. Can the approach be implemented?

4. Approach
    a. With the understanding that the trial design will be fully developed for the final, Stage 2, application review, is the preliminary design appropriate for the stated goals of trial and the indication?
    b. Are novel methods, assays, or approaches proposed?
    c. Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?
    d. Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria been addressed?
    e. Are the primary and secondary outcome measures appropriate?

5. Expertise
    a. Does the application demonstrate that the investigators have the relevant experience and expertise in the subject matter and clinical trial execution?

Composition of Objective Review Panel

The review of applications is carried out by a panel of experts with complementary knowledge of multiple areas related to the proposed study subject matter and the conduct of clinical trials such as pharmacokinetics, biological mechanisms, pharmaceutical industry development, and other relevant scientific and clinical expertise. NIH program officials attend the review meetings to provide programmatic input. Summary statements of the review panel meetings will not be made available. However, feedback on the Independent/Objective Review and the NINDS decision on the application are provided to applicants. Appeals are not allowed.

Decision Process

NINDS will select applications based on their technical merit, including consideration of the issues identified during independent review and relevance of the proposed project to program priorities. Projects selected for priority for Stage 1 by NINDS will be invited to submit a Stage 2 application to be considered for funding and project implementation within the STEP program in the NIH StrokeNet.