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 2 Protocol Application (OT2)**
Activity Code	OT2: Application for an Other Transaction Agreement
Research Opportunity Number	OTA-24-010
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 2 Protocol 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 systems of care for EVT, to be conducted within the StrokeNet Thrombectomy Platform (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 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 RCC 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" 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.

Objectives

Under this ROA, the NINDS will accept Stage 2 Protocol Applications to fund 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 to be conducted within STEP program within the NIH StrokeNet. STEP clinical trial applications are accepted and reviewed in a two-stage process. Stage 1 Preliminary Applications, submitted under ROA (OTA-24-009) may be submitted by academic investigators, industry applicants, private institutions, or nonprofits. At Stage 2, the NIH StrokeNet NDMC is the applicant of record. The NIH StrokeNet NDMC will work with the Stage 1 applicants to obtain relevant information. Stage 2 Protocol Applications are accepted by invitation only and involve the submission of more detailed information on the proposed clinical trials and related activities. Please refer to Section 5: Application Information and Submission for detailed information.

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.

Section 3. Potential Award Information

NIH funds to conduct the study will be awarded directly to the NIH StrokeNet NDMC (through an Other Transaction Agreement) only after successful completion of Stage 1 and 2 of the application and review process. The NIH StrokeNet NDMC then administers the funds to other NIH StrokeNet and STEP components and to the preliminary asset application applicant as appropriate.

OT clinical trial applications may not include requests for the funding of activities covered under Stroke-Net NCC, NDMC, or RCC agreements, which provide funds for the NIH Stroke-Net infrastructure.

It is anticipated that there will be multiple concurrent asset clinical trials funded through OT clinical

trial parent application and supplements.

Authority:

This Research Opportunity Announcement (ROA) is issued with the goal to enable stroke thrombectomy platform trials to answer questions using a seamless rolling approach within the existing NIH StrokeNet infrastructure. 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). Funds resulting from this ROA will be provided by modification to OT Agreement No. 1OT2NS129366-01.

Section 4. Eligibility

Organizations

The following entities are eligible to apply under this ROA if selected after the STEP Stage 1 review:

The NIH StrokeNet NDMC (located at the Medical University of South Carolina).

Eligible Individuals (Program Director/Principal Investigator): Any individual(s) identified by NIH StrokeNet NDMC (located at Medical University of South Carolina) as having the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s). Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

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 ROA (OTA-24-009) 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 this ROA, 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 2 Protocol Application Information:

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 appropriate use of any funds awarded and 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 as a signatory to the Other Transaction agreement.
- The total cost proposed.

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 Protocol Application

The Clinical Trial Protocol Application must include following information.

- Clinical Trial Protocol- The NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template) (NOT-OD-17-064) will be used as a guideline for the protocol. This template will be adapted to reflect the asset and population to be studied. (typically not exceeding 20 pages in length, excluding references)
- A detailed Timeline and Milestones
- Statistical analysis plan (typically not exceeding 15 pages in length, excluding references)
- A detailed budget and budget justification as further explained below.

Letter of Support

If collaborations have been established, include letters of collaboration in the application that document the role of each collaborator. Letters should be combined into a single PDF.

Budget Information

The budget shall contain sufficient information to allow the Government to perform a basic analysis of the proposed cost of the work. This information shall include the amounts of the line items of the proposed cost. These elements will include the following elements by milestone event and/or proposed period as applicable:

- Direct Labor – Individual labor category or person, with associated labor hours and unburdened direct labor rates;

- Indirect Costs – Fringe Benefits, F&A, etc. (Must show base amount and rate). Offerors must submit a copy of their most recent indirect cost rate agreement negotiated with any federal audit agency, if applicable.

- Travel – Separate by destinations and include rationale for travel, number of trips, durations - number of days, number of travelers, per diem (hotel and meals in accordance with the Federal Travel Regulations), airfare, car rental, if additional miscellaneous expense is included, list description and estimated amount, etc.

- Subawardee – A separate detailed budget shall be submitted by each proposed subawardee. The subawardee's proposal should include on company letterhead the following:

    - Complete company name and mailing address, technical and administrative/business point of contacts, email address, and telephone number.

    - Include the DUNS number and CAGE code.

    - A commitment letter from the proposed subcontractor's business official that includes:

        - Willingness to perform as a subawardee for specific duties (list duties).

        - Proposed period of performance.

        - Supporting documentation for proposed costs (personnel documents to verify salaries, vendor quotes for equipment, negotiated indirect cost rate agreement.

- Consultants – For proposed consultants, provide draft consulting agreement or other document which verifies the proposed loaded daily/hourly rate and labor category.

    - Written verification from the consultant of their proposed rate, along with a statement that it is their usual and customary rate charged to other customers.

    - Description of the work to be performed by the consultant and direct relevance to the work. Include information on why this expertise is not available in-house.

- Materials & Supplies – Should be specifically itemized with costs or estimated costs. Include supporting documentation, i.e., vendor quotes, catalog price lists, and past invoices of similar purchases.

- Other Direct Costs – Especially any proposed items of equipment. Equipment generally must be furnished by the Offeror. Justifications and vendor quotes must be provided when Government funding for such items is sought.

Salary Rate Limitation

- Pursuant to current and applicable prior NIH appropriations acts, it is anticipated that Offerors submitting applications under this ROA will be subject to a salary rate limitation on funds used to pay the direct salary of individuals.

- Congress has stipulated in NIH appropriations act that, under applicable extramural awards appropriated funds cannot be used to pay the direct salary of an individual at a rate in excess of the Federal Executive Schedule Level II.

- For purposes of the salary rate limitation, the terms “direct salary,” “salary,” and “institutional base salary,” have the same meaning and are collectively referred to as “direct salary”, in this clause. An individual's direct salary is the annual compensation that the Offeror pays for an individual's direct effort (costs) under the award. Direct salary also excludes fringe benefits, overhead, and G&A expenses (also referred to as indirect costs or facilities and administrative [F&A] costs). Note: The salary rate limitation does not restrict the salary that an organization may pay an individual working under an NIH award; it merely limits the portion of that salary that may be paid with Federal funds.

- The salary rate limitation also applies to individuals under subawards.

- See the salaries and wages pay tables on the U.S. Office of Personnel Management Web site for Federal Executive Schedule salary levels that apply to the current and prior periods.

Data Management and Sharing Plan (no more than 2 pages)

In accordance with NIH Policy for Data Management and Sharing, describe how the proposed data generated from the project will be managed and shared. For elements to include in the Data Management and Sharing Plan, please see Data Management & Sharing Policy Overview, writing a Data Management & Sharing Plan | Data Sharing (nih.gov) and NOT-OD-21-014: Supplemental Information to the NIH Policy for Data Management and Sharing: Elements of an NIH Data Management and Sharing Plan. NIH respects and recognizes Tribal sovereignty and American Indian and Alaska Native (AI/AN) communities’ data sharing concerns. For research teams working with Tribes and AI/AN communities, please refer to NOT-OD-22-064: Supplemental Information to the NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data.

Section 6. Independent, Objective Review Information

The Stage 2 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. How will successful completion of this clinical trial change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
    b. Does the protocol mitigate weaknesses/critical barriers or fill gaps in prior research?
    c. If the aims of the protocol are achieved, how will scientific knowledge or treatment development for the condition under study be advanced? If successful, will the data support the conduct of later phase clinical trials if appropriate?
    d. Does the protocol otherwise incorporate innovative aspects, such as in concepts, design, approaches, or methodology?
    e. Will any innovative elements enhance the study's ability to generate data that will move the field forward?

2. Approach
    a. Is the overall approach well-reasoned, feasible, and appropriate to accomplish the study specific aims?
    b. Will the approach generate balanced, unbiased data?
    c. Are potential problems identified and addressed? Are alternative strategies and benchmarks for success presented?
    d. Will the protocol provide data that will inform a subsequent go/no-go decision about whether to move the asset forward for further development and later phase clinical trials?
    e. Does the protocol identify research-related risks and provide ways to minimize those risks?
    f. Are study population selection and individual subject eligibility equitable in terms of sex, gender, race, ethnicity, age, etc.? Are any exclusions justified by scientific or safety needs of the study? If applicable, will the study be able to address outcome differences due to these factors?
    g. Does the protocol adequately address the following?:
        i. Study design: does the study design enable efficient generation of clear, relevant data to address primary and secondary outcomes and inform the study hypothesis? Are the treatment regimen (e.g. for drugs: dose, duration, route of administration; for devices: application, exposure session duration, number of sessions) and duration of the study and study phases appropriate and justified by available data?
        ii. Is the study adequately powered? Are the study cohorts well-defined, appropriate, and informative? Are randomization, masking, and controls appropriately addressed?
        iii. Are the plans for participant recruitment, enrollment, and retention acceptable? Can the study population feasibly be obtained?
        iv. Are the planned statistical approach and analyses appropriate? Is the plan for data management adequate? Can the study and data analyses be completed in a timely manner?
        v. Are the plans for quality control, quality assurance and quality monitoring adequate?
    h. Is the timeline described in detail, taking into account start-up activities? Is the projected timeline feasible and well-justified?
    i. Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of barriers or complications during

implementation)?

3. Expertise and Resources
    a. Will the study benefit from being conducted within the STEP network environment?
    b. Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed?
    c. Does the application adequately address the capability and ability to conduct the trial at the proposed site(s) or centers?
    d. Is there evidence of the ability of the individual site or center to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and (4) operate within the proposed organizational structure?
    e. 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?
    f. 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 and considerations:

As applicable for the project proposed, reviewers will evaluate the following additional criteria and considerations:

Protections for Human Subjects

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

Inclusion of Women, Minorities, and Individuals Across the Lifespan

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

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.

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

Note: Effective for due dates on or after January 25, 2023, the Data Sharing Plan and Genomic Data Sharing Plan (GDS) will not be evaluated at time of review. Reviewers will comment on whether the Resource Sharing Plan(s) (i.e.; Sharing Model Organisms) or the rationale for not sharing the resources, is reasonable.

Authentication of Key Biological and/or Chemical Resources:

For resources 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.

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 for presentation to the NINDS Advisory Council and approval by the NINDS Director before award of Other Transaction funding and project implementation within the NIH Stroke-Net.