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	**Platform Trials of Thrombectomy in Acute Stroke – Application to implement the master protocol with indication expansion in the StrokeNet Thrombectomy Platform (STEP)**
Activity Code	OT2: Application for an Other Transaction Agreement
Research Opportunity Number	OTA-23-009
Related Notices	
Key Dates:	Posted Date: 5/10/2023
	Open Date (Earliest Submission Date): 5/15/2023
	Application Due Date(s): 6/12/2023
Scientific Contacts	Scott Janis, PhD, Program Director StrokeNet, NINDS janiss@ninds.nih.gov.

Content by Sections

Section 2. Objectives of this Opportunity

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. 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 350 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 thrombectomy in specific subgroups of ischemic stroke patients.

To address this need, NINDS initiated the infrastructure of the Stroke Thrombectomy Platform (STEP) platform in 2022 within the existing NIH StrokeNet to develop a master protocol and statistical analysis plan that would enable platform trials to 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 management approaches, and that will also open the door to testing neuroprotectant strategies in an efficient, timely, and cost-effective manner.

This ROA will allow completion of the STEP platform infrastructure to implement the master protocol and the initial trials to expand the indications of endovascular therapy. The infrastructure application must include the broad governance of the STEP platform; integration of essential STEP cores, including but not limited to recruitment, data transfer among operating components, image processing and data management, endovascular intervention quality control, statistical design, consultation with external stakeholders; and advisory oversight of expert advisory groups to facilitate implementation of STEP trials in Endovascular therapy (EVT) performance, concomitant medical therapies added to EVT, novel EVT devices and systems of care for EVT. Additionally, the scope of this ROA includes a proposal for handling a pipeline of trials for indication expansion to map subsets of EVT treatment in patients with large and medium vessel occlusions and determine the extent that EVT would be efficacious, neutral, or potentially harmful to different subgroups of this patient population without sufficient randomized clinical trial evaluation. Plans included in response to this ROA must cover activities for up to the next five years with the flexibility to add future trials through modification of the Other Transactions agreement.

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

The purpose of this research opportunity announcement (ROA) is to fund the full implementation of the STEP platform and provide funding to initiate domain trials to expand the indications of endovascular therapy. The application will implement an FDA-approved master protocol and provide the infrastructure organization within the NIH StrokeNet to conduct future STEP domain platform trials.

Scope

The STEP-Platform is designed to test the efficacy and safety of clot retrieval in 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 STEP-platform 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

Authority:

This Research Opportunity Announcement (ROA) is issued with the goal of initiating a master protocol and SAP to enable stroke thrombectomy platform trials to answer questions using a seamless rolling approach within the existing NIH StrokeNet infrastructure. OT Agreements are used to fund clinical trials to be executed through the NIH StrokeNet Platform Program, pursuant to 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:

The 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

Submission Information

Applications to the NIH Stroke-Net Thrombectomy Platform must be submitted via eRA COMMONS no later than the "application due date" shown under the "Key Dates" section of this announcement. Use this ROA number when submitting the application in NIH eRA Commons.

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 and the budget proposed. Full applications must be submitted by the due date, in text-recognizable PDF (Adobe) format, use 11-point font with 1" margins and be single-spaced.

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

- Number and title of this ROA
- Project title
- The Awardee's
  - Legal entity name
  - Address and contact information
  - SAM # and expiration date
  - DUN # 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 Awardee's Business Official, the person authorized to negotiate and bind the Awardee as a signatory to the Other Transaction agreement.
- The total cost proposed

Application Requirements

Abstract ("Abstract.pdf"; 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 ("SpecificAims.pdf"; 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 ("KeyPersonnel.pdf"; no page limit)

All Key Personnel who are major contributors to the EVT platform must provide an NIH Biosketch whether or not they are budgeted. Do not include NIH Biosketches for key personnel at the StrokeNet NCC, the NDMC, or at the clinical performance sites unless they have a separate specific role in the proposed study.

Design/Research Plan ("ResaeachPlan.pdf"; no more than 12 pages)

The research plan should include the following:

- Plans for the initiation and implementation of the master protocol and the master statistical analysis plan (SAP) for including future domain specific trials in the STEP platform
- Plans for including the National Clinical Coordinating Center, the Regional Coordinating Centers, non-StrokeNet elements, and all cores and advisory groups necessary for the broad governance of the STEP platform
- Description of the indication expansion platform trial to expand the indications of endovascular therapy, including a summary of the following
    - A description and rationale of the study design.
    - Rationale for the study population and why it is an appropriate group to answer the question under study.
    - Rationale for selection of the study outcomes and endpoints.
    - A list of subject inclusion/exclusion criteria.
    - A discussion of the evidence regarding whether clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected and plans for valid design and analysis.
    - A description of all assessments, including clinical, laboratory, physiological, behavioral, patient-centered, or other outcomes addressing the primary and secondary research questions.
    - A discussion of potential biases and/or challenges and how they will be addressed.

- A detailed Timeline and Milestones

Other Document attachments (no page limit)

- Include Master Protocol and the appendix to the protocol for the indication expansion platform trial

- Include the Master Statistical Analysis plan and the SAP for the domain specific appendix.

Resource Sharing plan ("Datasharing.pdf"; no more than 3 pages)

Include description of the data sharing plan that results in the generation of scientific data generated through this proposal. This attachment is limited to three pages.

Budget information (no page count)

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.

Section 6. Independent, Objective Review Information

The application will undergo an objective technical review by independent reviewers.

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 of the research plans for the EVT platform and indication expansion domain trials for NINDS consideration.

The Independent 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.

Independent/Objective Review Criteria

1. Significance
    a. Do the applicants have an achievable and appropriate plan to implement the master protocol and the master statistical analysis plan to address an unmet therapeutic need in endovascular therapy?
    b. Does the master statistical analysis plan efficiently map data elements with the American Heart Association and American Stroke Association Get with the Guidelines® (GWTG) registry and with the NeuroVascular Quality Initiative-Quality Outcomes Database (NVQI-QOD)?
    c. Do the applicants provide a plan to seamlessly include future EVT clinical trial questions into the platform?
    d. Do the proposed clinical trials to expand the indications of endovascular therapy address important or critical barriers in the existing treatments to progress the field?
    e. Will these trials, when completed, have an impact on the field and exert significant improvements in endovascular therapy?

2. Innovation
    a. Does the design/research plan include innovative elements, as appropriate, that enhance its potential to advance scientific knowledge or clinical practice?
    b. Does the application otherwise incorporate innovative aspects, such as in concepts, design, approaches, or methodology?
    c. Will any innovative elements enhance the platform's ability to generate data that will move the field forward?
    d. Is the research plan novel?
    e. Will the research plan be able to refine patient groups that do or do not benefit from thrombectomy?

3. Approach
    a. Is the overall approach well-reasoned, feasible, and appropriate to implement the STEP platform?
    b. Does the application implement an FDA-approved master protocol?
    c. Is the approach to include new domain platform trials will be included?
    d. Will the approach generate balanced, unbiased data?
    Are potential problems identified and addressed? Are alternative strategies and benchmarks for success presented?
    e. Is the flow of human subjects' data, its structure, management, quality control, security, and access clearly laid out?
    f. Does the database incorporate established data standards and common data elements (CDE's)?
    g. Does the application identify research-related risks and provide ways to minimize those risks?
    h. Are study population selection and individual subject eligibility equitable in terms of

sex, gender, race, ethnicity, and age? 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?

i. Does the protocol for indication expansion 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 hypotheses?
    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?
j. Is the study timeline feasible?

4. Environment
    a. Do the applicants have the resources/infrastructure to complete the project?
    b. If identified, do any identified clinical sites provide an environment that can contribute to successful conduct of the study?

5. Investigator(s)
    a. Do the applicants have the necessary expertise to implement the STEP Platform?
    b. Does the application include the necessary expertise the implement the indication expansion trials?
    c. Do all identified investigators have leadership support and institutional governance and organizational structure appropriate to lead the STEP Platform?
    d. If the application includes a multiple-PI plan, is the role of each PI clear and is their role in the platform clearly justified?

Additional Review Criteria and considerations:

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

<u>Timeline</u>

a. Is the timeline for the indication platform trials described in detail and is it feasible and well-justified (i.e., are the sufficient details (enrolment rate, follow-up, etc.) to demonstrate the project is achievable in the planned study period?
b. Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of barriers or complications during implementation)?

<u>Protections for Human Subjects</u>

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

Review will be carried out by an established panel of experts with complementary knowledge of multiple areas related to the proposed study subject matter and the conduct of clinical trials 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 consider funding based on the scientific and technical merit, including consideration of the issues identified during the external review and the relevance of the proposed project to program priorities for presentation to the NINDS Advisory Council for their approval before award of Other Transaction funding and project implementation within the NIH Stroke-Net.