Section 1. Overview Information

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<td>National Institute of Neurological Disorders and Stroke (NINDS)</td>
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<td>Research Opportunity Title</td>
<td>Platform Trials of Thrombectomy in Acute Stroke (OT2)</td>
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<tr>
<td>Activity Code</td>
<td>OT2: Application for an Other Transaction Agreement</td>
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<td>OTA-22-001</td>
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<td>Key Dates:</td>
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<tr>
<td>Scientific Contacts</td>
<td>Scott Janis, PhD, Program Director StrokeNet, NINDS <a href="mailto:janiss@ninds.nih.gov">janiss@ninds.nih.gov</a>.</td>
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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. 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 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 is interested in establishing master protocols to enable platform trials that answer the above questions using a seamless rolling approach to be conducted within the existing NIH StrokeNet infrastructure. Trials that further refine patient groups that do or do not benefit from mechanical thrombectomy, and using which management approaches, will also open the door to testing neuroprotectant strategies in an efficient, timely, and cost-effective manner.

This ROA will establish the groundwork to include the master protocol for platform trials with the NIH StrokeNet, including the following activities: plan to create a master protocol that can be incorporated in the Stroke Network that is ready for Central Institutional Review Board (cIRB), Food and Drug Administration (FDA) and Data and Safety Monitoring Board (DSMB) approvals; plan to create a master statistical analysis plan (SAP) for the analysis structure for the platform; establish relationships and map common data elements (CDE) 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) for the statistical design to be included in the master protocol, and establish contracts with 2-3 performance sites with data use agreements to test the data transfer process. It is estimated the start-up process for these activities will require 6-9 months.

**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 master contract 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 establish the initial infrastructure for the master protocol to run platform trials of thrombectomy and related questions in acute stroke management in the NIH StrokeNet. To effectively run the Endovascular Trials (EVT) platform within the NIH StrokeNET, NINDS requires the existing infrastructure of the network be used and coordination of the activities be organized through the existing data coordinating structure of the NIH StrokeNet.

The NIH StrokeNet EVT platform application will be prepared by the National Data Management Center (NDMC) and will include:

- Plans for the Start-up Activities to include development of the master protocol and SAP
- Plans for including the National Clinical Coordinating Center, the Regional Coordinating Centers, and non-StrokeNet elements
- A detailed Timeline and Milestones
- A detailed Start-up Budget and budget justification as further explained below.

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.

Scope
Section 3. Potential Award Information

Authority:
This Research Opportunity Announcement (ROA) is issued with the goal of developing and initiating a start-up plan for the establishment of 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).

Section 4. Eligibility

Organizations
The following entities are eligible to apply under this ROA: The NIH StrokeNet National Data Management Center.

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

Section 6. Independent, Objective Review Information

The start-up plans will undergo objective review by Program staff at NINDS.

Administrative review is an assessment of scientific or technical merit of applications by individuals with appropriate scientific and/or human subjects research program management knowledge and expertise. Conflicts-of-interests of review members are appropriately managed during the review process in accordance with standard NIH policies. The review provides information essential to ensuring the submitted application meets the needs of the program using the criteria delineated below following a review that is conducted in a fair, objective manner free of prejudices and biases.

Reviewers provide individual assessments of the likelihood for the start-up plan to lead to successful establishment of a master protocol for platform trials of thrombectomy and related questions for NINDS consideration.

The reviewers will only consider the review criteria below in their individual assessments of merit. An application does not need to be strong in all categories to be judged likely to have major impact.
Independent/Objective Review Criteria

1. Do the applicants present an achievable plan to develop the master protocol that can be submitted for the necessary approvals by the FDA, cIRB, DSMB?
2. Do the applicants have an acceptable plan for developing the master statistical analysis plan and to map data elements with the GWTG and NVQI-QOR registries?
3. Do the applicants have the necessary expertise to complete the project?
4. Do the applicants have the resources/infrastructure to complete the project?
5. Is the flow of human subjects’ data, its structure, management, quality control, security, and access clearly laid out?
6. Does the database incorporate established data standards and CDE’s?
7. Is the issue of identifiers addressed?
8. Are privacy protections addressed? Is the proposed timeline for deployment acceptable?
9. Is the proposed start-up budget justified by the proposal?

Additional Review Criteria and considerations:

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

Timeline

a. Is the timeline described in detail, taking into account start-up activities? Is the projected timeline feasible and well-justified?
b. Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of barriers or complications during implementation)?

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 start-up activities.

Composition of Objective Review Panel

Review of the start-up plan will be conducted by NIH program staff. Summary statements of the review meeting will not be made available. However, feedback on the Independent/Objective Review and the NINDS decision on the application are provided to the applicant.

Decision Process

NINDS will select applications based on their technical merit, including consideration of the issues identified during the administrative review and 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.