SOP Number: ADM 27
SOP Name: Management of StrokeNet Trials with International Sites
Effective Date: 09/24/2024

1. POLICY

The purpose of the Standard Operating Procedure (SOP) is to describe the management, best practices and resources for initiating and conducting a National Institutes of Health (NIH) StrokeNet clinical trial in countries outside of the United States (OUS).

2. DEFINITIONS AND ABBREVIATIONS

CRO	Contract Research Organization
ESC	Extramural Science Committee
GAINS	Global Alliance of Independent Networks
IP	Investigational Product
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OUS	Outside of the United States
PI	Principal Investigator
PS	Performance Site
RCC	Regional Coordinating Center
SOP	Standard Operating Procedure
SS	Satellite Site
StrokeNet	NIH StrokeNet Network

3. SCOPE

This SOP applies to all investigators, staff, subcontractors or other entities associated with StrokeNet who manage, oversee, and conduct NIH StrokeNet research OUS.

4. PROCEDURES

The NIH StrokeNet facilitates the conduct of multi-site clinical trials by maintaining a network of Regional Coordinating Centers (RCC), Performance Sites (PS), Satellite Sites (SS) and their investigators

within the US. Non-network sites may also participate in StrokeNet trials within and outside of the US. A trial may elect to enroll participants from OUS sites to allow timely trial completion.

This SOP should be used by StrokeNet personnel and affiliates as a guide for initiating and conducting international StrokeNet trials.

A. International Component Determination

A prime principal investigator (PI) should identify whether to include OUS sites when the initial estimate for number of sites is made during the grant concept development phase to facilitate appropriate budgetary planning. Prime PIs should consider the following reasons for OUS sites as guidance when making their determination:

I. Acute trials requiring more than 40-50 sites.
II. Prevention or recovery trials requiring more than 80-100 sites.
III. A complex trial design that may require additional or specific resources to conduct.
IV. OUS sites with track records of excellent recruitment in prior similar trials, or in trials recruiting similar populations.
V. Feasible conduct of the trial in a particular country or countries.
    a. Consider contracting, Investigational Product (IP) availability and distribution, and data privacy issues.
    b. Consider ability to utilize a Contract Research Organization (CRO) for managing these OUS country processes.

Global Alliance of Independent Networks focused on Stroke trials (GAINS) may be a useful resource for PIs. GAINS was designed to accelerate the pace and success of stroke clinical trials by enhancing communication between leaders and participants of funded as well as developing national stroke trial networks. It allows for identifying OUS sites and funding partners, including contact information and links for other national networks, and an opportunity to share information about trials seeking international collaboration, such as at quarterly Global Trials Forums or on the webpage: https://www.globalstroketrials.org.

B. Budgeting

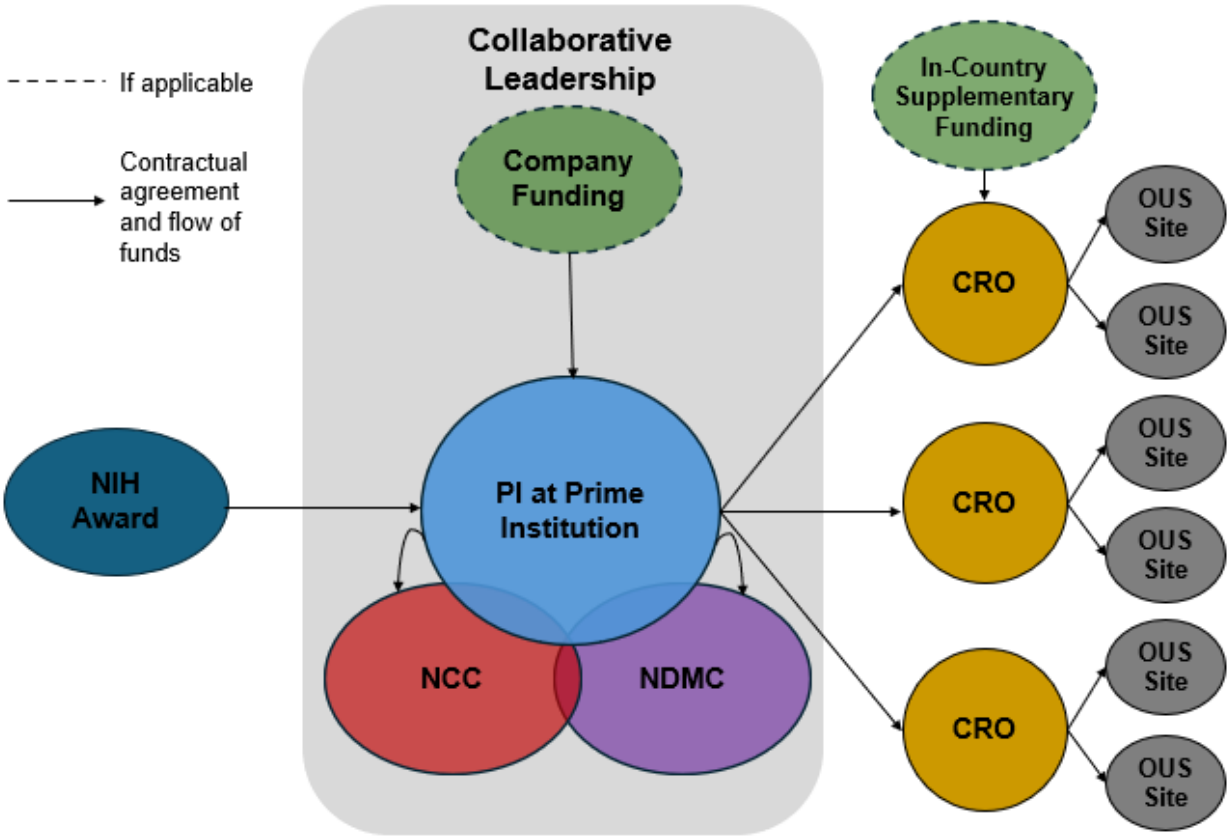
Discussion with StrokeNet and National Institute of Neurological Disorders and Stroke (NINDS) leadership regarding inclusion of OUS sites is a requirement prior to submitting the concept synopsis and preliminary budget to NINDS Extramural Science Committee (ESC) for approval to submit a full grant application. Investigators should consider sourcing supplementary funding from OUS entities to provide support for country-specific operations, and NINDS may require this for approval.

If the prime PI determines that the trial needs to expand internationally after the award has been granted, there must be sufficient funds remaining in the budget, or supplemental funds available to

support the additional efforts from the country-specific academic or commercial CRO, NCC, NDMC, imaging, pharmacy and other collaborative groups. Investigators can expect their trial budgetary needs to increase if an international component is added ad hoc. This is to support additional country-specific clinical coordination, data management, and other relevant activities, such as investigational product shipping and distribution. Creative solutions to bridge the gap between the awarded funds and the new budgetary needs may include partnering with colleagues in the additional country to seek additional sources of grant funding, or using residual indirect funds associated with site payments (i.e., if allowable rate is lower in OUS country compared to US) towards the newly incurred expenses. Determining how to use unspent monies to this end should be in consultation with the NINDS Program Official as early as possible. For efficiency and a higher likelihood of success, it is highly encouraged that investigators make appropriate arrangements prior to grant submission if OUS sites are anticipated at the outset.

C. Trial Operational Structure

Figure 1. Model for typical OUS trial operational management



The prime PI remains responsible for the overall conduct of the trial, however certain tasks may be delegated to OUS CRO(s). The use of a country or region-specific CRO to manage OUS trial operations is typically required. Research services are outsourced to CRO groups who may be independent entities or may be affiliated with a university or academic organization. In some cases, a CRO with international presence may take on facilitation of OUS sites. Country-specific presence allows for understanding of local context, in terms of contracts, currencies, competent authorities and ethics boards, and more time and cost-effective translation and clinical monitoring when applicable. The Prime PI institution is responsible for supervising and subcontracting directly with CROs. In some circumstances, when feasible and with additional funding, the NCC for NIH StrokeNet may take on this responsibility. Additionally, it may be helpful to have a designated OUS PI as well as country-specific national leads to serve as champions for the trial during investigator meetings, etc.

Several OUS CROs have participated in prior StrokeNet trials and performance data such as start-up timeliness will be available. For CROs new to StrokeNet, the trial PI team should determine if the CRO has the capability to manage all clinical coordination including contracting, site payments, site communication and training, clinical monitoring, regulatory activities such as delegation of authority to maintain local competent authority and ethics compliance, and translation if applicable.

Note that data management and statistical support would remain with the StrokeNet NDMC, although additional funding may be needed to accommodate OUS aspects of the trial.

D. Start-up

The NIH StrokeNet International Start-up Checklist, included in the attachment section of this SOP, should be referenced for a description of tasks required to initiate a trial at OUS sites. This checklist is to be used as a guide and may not be an inclusive list of start-up activities.

In addition to the CRO(s) identified at the outset, pharmacy depots, laboratories and other collaborative groups may need to be identified to facilitate relevant OUS operations. These entities are critical for start-up therefore the relevant regulations and potential barriers to expedient contractual agreement execution in specific countries should be well understood. Trial PIs may consult with NCC and NDMC leadership and consider leveraging standing partnerships with these OUS entities.

E. Site Selection

OUS sites that have participated in prior StrokeNet trials will have performance data such as start-up timeliness, recruitment and data quality metrics available in WebDCU™. For OUS sites new to StrokeNet, the trial team should consult with the CRO to determine if a particular site is an appropriate candidate for site selection.

F. Regulatory Considerations

CROs will be asked to provide current local clinical trial authorizations, ethics board approvals and informed consent documents, and annual ethics board review documentation to be maintained in WebDCU™. Additional documentation may be required to confirm OUS ethics board review dates if not in alignment with the review period in the US.

The trial's prime PI, as the sponsor, should have access to any regulatory documents that are not maintained in WebDCU™, and are filed by CROs through another central system or are filed at the site level.

G. Protocol Considerations

Trial PI(s) should consider differing clinical practice and regulatory contexts between US and OUS sites, and across OUS sites, at the outset when designing the trial protocol. Consideration should be paid to using language that will allow the use of a single protocol for all countries (e.g., use of broad terms like "relevant ethics committees") and use of placeholder eligibility criteria with expanded details in the Manual of Procedures (MOP) (e.g., "reduced renal function below the country-specific drug label thresholds – see MOP section XYZ for details").

5. APPLICABLE REGULATIONS AND GUIDELINES

ICH E6(R2) Guidelines for Good Clinical Practice

21 CFR 56 Institutional Review Boards

6. REFERENCES TO OTHER APPLICABLE SOPS

7. ATTACHMENTS AND REFERENCES

NIH StrokeNet International Start-up Checklist

Proposal Development Process Flowchart - https://nihstrokenet.org/docs/default-source/default-document-library/proposal-development-process-flowchart-6-1-2023.pdf?sfvrsn=0

8. DOCUMENT HISTORY

Version	Description of Modification	Completion Date	Issue Date	Effective Date
1.0	Final	2024-09-24		

NIH StrokeNet Network

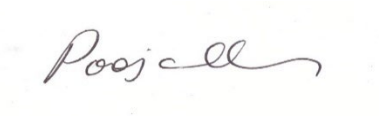
Standard Operating Procedure (SOP)

Management of StrokeNet Trials With International Sites

Version 1.0

ADM #27

Reviewed and Approved by:



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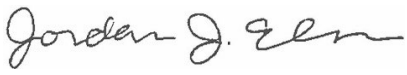

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