NIH StrokeNet Network
Standard Operating Procedure

SOP Number: ADM 17
SOP NAME: NIH StrokeNet Organization and Governance
Effective Date: 6-Nov-2015 (rev 18-Aug-2023)

1. POLICY

The purpose of NIH StrokeNet is to harness multidisciplinary stroke expertise to develop and conduct high-quality, multi-site trials, related biomarker validation studies, and ancillary studies focused on key interventions in stroke prevention, treatment, and recovery. This document is to provide definitions and explanations of the responsibilities for the components of the NIH StrokeNet Network (StrokeNet).

2. ABBREVIATIONS AND DEFINITIONS

CIRB	Central Institutional Review Board: Assumes the responsibility of approving, monitoring, and reviewing biomedical and behavioural research involving humans.
PS	Performance Site: An institution that is not legally affiliated with an awarded RCC, but which has agreed to serve and be wholly supervised by the RCC or SS as a network trial recruitment site.
CRF	Case Report Forms
CTA	Clinical Trial Agreement
CTSA	Clinical and Translational Science Awards: A program that aims to strengthen and support translational research by accelerating the process of translating laboratory discoveries into treatments, training new clinical and translational researchers, and engaging communities in clinical research efforts.
DSMB	Data and Safety Monitoring Board
EC	Executive Committee: A governance committee of StrokeNet
FDA	Food and Drug Administration
GCP	Good Clinical Practice: Is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
IDE	Investigational Device Exception: Allows the investigational device to be used in a clinical study to collect safety and effectiveness data
IND	Investigational New Drug: New drug or biologic that is used in a clinical investigation
MPI	Multiple Principal Investigators
NDMC	National Data Management Center at the Medical University of South Carolina (MUSC)
NCC	National Coordinating Center at the University of Cincinnati (UC)
PPI	Protocol Principal Investigator
RA	Reliance Agreement
RCC	Regional Coordinating Center: An institution designed and directly funded by the NINDS/NIH to provide leadership for the NIH StrokeNet on a regional level.
SS	Satellite Site: an institution named by an RCC as a part of its regional network that is not legally affiliated with the RCC but maybe delegated (via RCC standard operating procedures (SOPs) certain leadership responsibilities.
StrokeNet	NIH StrokeNet Network
WG	Working Group: A stroke domain review committee of StrokeNet

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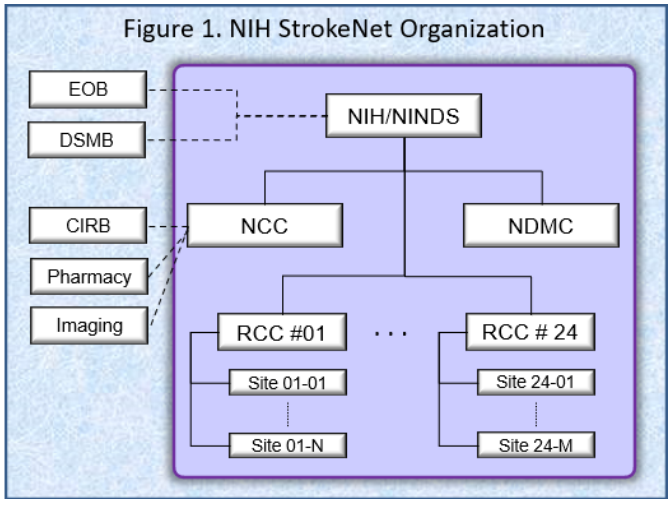
3. SCOPE

The information provided in this document applies to all internal and external StrokeNet interfaces.

4. Overall Network Structure and Components

The infrastructure (Figure 1) consisted of: (A) the National Clinical Coordinating Center (NCC) at the University of Cincinnati (UC) to provide overall leadership and coordinate activities including central IRB (CIRB), pharmacy, and now imaging activities; (B) the National Data Management center (NDMC) at the Medical University of South Carolina to provide data management and statistical collaboration; (C) 24-27 Regional Coordinating Centers (RCCs) affiliated with ~500 potential sites to recruit study participants and train future stroke researchers; and (D) the NINDS Project Scientist to provide scientific/administrative input. In addition, the NINDS has formed an External Oversight Board (EOB) that oversees its progress and advises its leadership on its overall direction, and the Data and Safety Monitoring Board (DSMB) that monitors study performance and participant safety.

Figure 1. NIH StrokeNet Organization



A. The National Coordinating Center (NCC) provides leadership for the StrokeNet infrastructure to facilitate rapid development and implementation of NINDS-funded stroke trials. Responsibilities of the NCC include but are not limited to:

1. Overseeing from conception to analysis/publication the implementation of multi-center clinical trials, biomarker validation, and ancillary studies conducted in the network.
2. Monitoring human subjects' protection and adequate women and racial and ethnic minority representation among subjects enrolled at network clinical sites. Coordinating and documenting all communication and reporting between the NCC, RCCs, central IRB of record, and local IRBs maintaining documentation of IRB initial approvals, amendment approvals, adverse events, and other reports.
3. Establishing standard Clinical Trial Agreements (CTA)s with NIH StrokeNet Satellites and Clinical Performance Sites. StrokeNet NCC has transitioned away from the use of Master Trial Agreements (only having CTAs) as this has proven to improve trial start-up time.
4. Coordinating all NIH StrokeNet governance activities listed in Section E of this document.
5. Coordinating study drug management, including but not limited to drug and placebo acquisition, delivery plan for bulk drug, secondary packaging/labeling/distribution/storage, blindedness testing, coordinating stability testing, accommodating expiration timelines, and drug accountability.
6. Coordinating management of centrally stored neuroimages collected in NIH StrokeNet studies.
7. Working closely with the NDMC in a collaborative and interactive manner.
8. Providing collaborative leadership to the clinical performance sites.
9. During the Conceptual Phase of each potential new network project, the NCC is responsible for:

a) Collaborating with RCC PD/PIs within the network to develop original stroke clinical trial, biomarker validation or ancillary study grant applications for submission to the NINDS for peer review.
b) Providing information necessary to potential investigators as they apply for funding by the NINDS (e.g., reviewing protocol synopsis and schedule of activities, creating project work scope and timeline, ensuring the feasibility of the proposed projects by analyzing the numbers of potentially eligible participants at the proposed sites and by including patient representatives in the conceptual process).
c) If needed, the NCC will support project PD/PIs in the IND/IDE submission

10. During the Planning Phase of approved network projects, the NCC is responsible for:
    a) Working with a project lead team of investigators to finalize the protocol and consent form.
    b) Collaborating with the NDMC to create case report forms (CRFs).
    c) Participating in the selection of additional sites as needed.
    d) Developing a written, detailed patient recruitment and community engagement plan, with attention to adequate racial and ethnic minority recruitment.
    e) Monitoring the IRB approval process and promoting rapid approval through a well-developed and complete document at the initial submission, and through rapid and comprehensive responses to any IRB comments or concerns.
    f) Collecting regulatory documents (1572 forms, curricula vitae, Good Clinical Practice [GCP] certifications, etc.).
    g) Finalizing details of per-patient payments to sites within approved budgets, developing site payment schedules, and finalizing subcontracts with sites per master trial agreements.
    h) Finalizing study drug packaging and labeling.
    i) Holding virtual investigator meetings and ensuring initial study personnel complete training for GCP and protocol adherence.
    j) Working with the NDMC as they establish a trial database.
11. During the Implementation Phase, the NCC is responsible for:
    a) Overseeing the enrollment of eligible subjects.
    b) Tracking enrollment and retention, developing outreach interventions as needed, and reporting progress to the NINDS.
    c) Distributing study drug to centers.
    d) Working with sites to ensure appropriate protocol implementation and adherence to protocol and GCP.
    e) Answering queries from the centers regarding protocol, drug dose adjustments, adverse events, premature withdrawals, etc.
    f) Conducting site visits, as needed.
    g) Supporting the NDMC in their monitoring and data quality assurance procedures. Coordinating activities with SIREN or other international consortia and sites as warranted in the enrollment of subjects into the clinical trial.
12. During the Analysis and Publication Phase, the NCC is responsible for:
    a) Assisting the NDMC and network centers in resolving final queries, finalizing reporting to the FDA and IRBs.
    b) Coordinating the communication of the trial results to the investigators, patients, and public.

c) Working with the NDMC and network investigators in the publication of the primary and, if applicable, secondary manuscripts.

B. The National Data Management Center (NDMC) supports protocol data management, ensures data quality control (including data monitoring), and undertakes interim monitoring, analyses, and reporting for the NCC, the NINDS, and Data and Safety Monitoring Boards (DSMB's). The NDMC also initiates and coordinates activities that promote standardization of data elements using the NINDS Stroke Common Data Elements and supports an aggressive sharing policy for de-identified data. The responsibilities of the NDMC include but are not limited to:

1. Data Management
   a) Maintain a network NDMC Standard Operating Procedures (SOPs) for all aspects of data management used in the current network.
   b) Adhere to a scope of work plan developed in collaboration with the NCC that clearly delineates NCC and NDMC tasks, respectively, and document communication plan.
   c) During the Conceptual Phase of a new network project, the NDMC is expected to:
      i. Provide information and/or collaborate with RCC PD/PIs within the network to develop original stroke clinical trial, ancillary projects, or biomarker validation grant applications for submission to the NINDS.
      ii. Provide information and/or collaborate with potential investigators or companies outside of the network as they apply for NINDS funding.
   d) During the Planning Phase of approved network projects, the NDMC will:
      i. Work with the project lead team of investigators to finalize data management aspects of the protocol.
      ii. Work with the project investigators and NCC to create a database for each trial in a timely manner.
      iii. Develop Case Report Forms (CRF's).
      iv. Finalize randomization scheme/process.
      v. Develop a data quality assurance plan.
      vi. Develop a data monitoring plan.
   e) During the Implementation Phase of approved network projects, the NDMC will:
      i. Support all data management aspects of trials implementation
      ii. Provide efficient project management for data management projects.
      iii. Promote standardization and harmonization of data collection across trials to include using the NINDS Stroke Common Data Elements (CDE).
      iv. Work with the NCC to report and track trial status in terms of enrollment and retention.
      v. Transfer data to statistician and others for interim analysis as needed, and at the end of follow-up, cleaning, and closing-out the database.

2. Data Quality Assurance - Oversee data quality control, including but not limited to regular data queries and data monitoring and cleaning to assure data completeness and quality.

3. Data Sharing - Support and promote rigorous data sharing after trial completion by preparing a final data set, with limited personal or de-identified health information, in a format appropriate for data sharing, for submission to a secure data repository after publication of the primary study results, or after 18 months, whichever comes first.

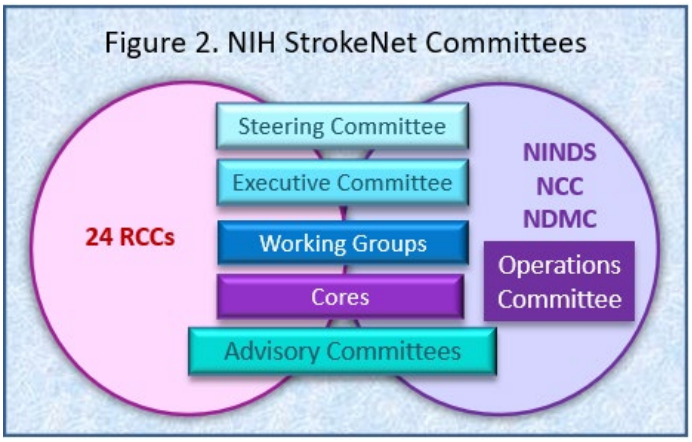
4. Monitoring - Identify experienced clinical research monitors to conduct site visits to monitor the quality of record keeping, source documentation, and the accuracy of data entry.
5. Statistical Support
   a) Include expertise in adaptive, Bayesian, or innovative statistical methodology necessary to provide statistical input into the potential design of adaptive Phase 2/3 clinical trials that could be done within the network, or expertise in using innovative adaptive methodology to assist in the design and/or analysis of studies that could efficiently compare multiple approaches or interventions.
   b) Provide statistical input to network investigators or to potential network project applicants at the request of the NINDS during the conceptual, pre-submission phase.
   c) Collaborate with the clinical investigators and project study statisticians in the oversight of interim and final analyses per protocol and in preparation of presentations of primary and secondary publications.
   d) Provide additional analyses at the request of the DSMB, the FDA, or the NINDS.

C. The Regional Coordinating Centers (RCC)s will have both clinical science excellence and specialized expertise in stroke management, a strong background in stroke research, and a proven ability to recruit stroke patients that include patients from various racial and ethnic minority groups. Each RCC is expected to have a multi-disciplinary collaboration that includes stroke specialists from neurology, pediatric neurology, emergency medicine, neurosurgery, neuroimaging, interventional radiology, neurointensive care, neurorehabilitation, other medical specialists, and emergency medical services. RCCs are expected to:

1. Propose, develop, and conduct protocols, recruit patients, and disseminate research findings.
2. Take part in multiple concurrent protocols and to recruit additional sites into their regional consortium as needed to enroll participants in a timely manner in NINDS-funded NIH StrokeNet trials.
3. Participate in a cooperative and interactive manner with one another and with the NCC.
4. Providing scientific leadership and regular communication to satellite centers regarding protocols and study progress.

D. National Institute of Neurological Disorders and Stroke (NINDS) will be responsible for organizing and providing overall support for the network. The NINDS Division of Clinical Research and the NINDS Grants Management will be responsible for the overall management of the network. In addition to regular grant stewardship, a NINDS Project Scientist will be involved substantially with the recipients as a NINDS partner and co-chair on the network's leadership committees, consistent with the Cooperative Agreement mechanism. The NINDS maintains the NIH StrokeNet DSMB that monitors all network trials and the External Oversight Board (EOB), comprised of an external group of experts, who reviews the network program and provides feedback to network investigators and the NINDS on a bi-annual basis.

E. NIH StrokeNet Governance: Figure 2 illustrates the StrokeNet governance committees and groups. Their members and responsibilities are as follows:



1. Executive Committee - Oversees strategic StrokeNet leadership and overall network management (monitor site performance, extra and intra network collaborations, training, new study opportunities).

A. Membership**:** Standing members are the NINDS Project Scientist and NINDS Grants Manager, NCC MPIs, NCC Administrative Co-Directors, NDMC MPIs, NDMC Operations Director, Chairs of the Prevention, the Acute Stroke Treatment, and the Recovery and Rehabilitation Working Groups. Rotating members are three RCC PIs chosen in collaboration with NINDS for a three-year term. A current list of members is available from the NCC.

B. Meetings and Teleconference: Frequency**-** Bi-monthly teleconference and annual face to face meetings. Agendas will be provided, and minutes of the calls maintained by NCC. Attendance and participation will be recorded by NCC.

C. Sub-Committees:

1) Publication Committee and Data Sharing Committee

a) Membership- NCC MPIs, NDMC MPIs, NINDS Project Scientist, Chairs of the WGs, the PPI of each ongoing Trial within StrokeNet until the trial is completed. For publications related to the Cores' activities the chair and Co-Chair of the Cores will be ad hoc members.

b) Responsibilities: Developing and disseminating knowledge derived from StrokeNet and if appropriate, other network managed studies, updating or amending the Publication and Data Sharing Network SOPS/guidelines and in collaboration with trial PPIs–developing specific publication instructions. The committee does not have authority over individual study Publications Committees except where multiple StrokeNet trials are to be used.

c) Meeting Frequency: As needed in response to publication volume.

2. Steering Committee - Main governing body of the StrokeNet's scientific operation and conduct. All major StrokeNet decisions will be determined by majority vote of this committee. Each RCC, the NCC, the NDMC will provide one vote each. All decisions must be concurred by NINDS leadership.

A. Membership**:** NINDS Project Scientist and CL, NCC MPIs, NDMC MPIs, and RCC MPIs. A current listing of members is available from the NCC.

B. Meeting Frequency: Virtual Meetings will be scheduled monthly. Agendas will be provided, and minutes of the calls maintained. Attendance is mandatory but appropriate delegates may be appointed for unavoidable absences. Attendance and participation will be recorded by NCC.

3. Operations Committee - a non-governing committee that oversees all StrokeNet activities, operational issues, and monitors network performance.

A. Membership**:** NINDS Project Scientist, NINDS Grants Manager, NCC MPIs, Administrative Co-Directors, NDMC MPIs, NDMC Operations Director and Project Manager, key NCC personnel representing CIRB, central pharmacy and financial administration and contract services, protocol specific PIs and trial specified designees for StrokeNet trials. A current listing of members is available from the NCC.
B. Meeting Frequency**:** Virtual Meetings will be scheduled weekly. Agendas will be provided, and minutes of the calls maintained by NCC.

4. Working Groups (WG)s – Includes **Prevention, Acute Stroke Treatment, and Recovery and Rehabilitation**. The primary function of the WGs is to critique, refine and to assist in determining feasibility for clinical concepts submitted to StrokeNet for review by NINDS or trial proposals developed by StrokeNet investigators.

A. Membership: Each WG has a Chair, Co-Chair, NDMC appointed representative, Imaging Core Representative, Patient Advocacy Core Representative, Diversity, Equity, and Inclusion (DEI) Core representative, volunteer RCC Manager representative, volunteer RCC PIs appointed by the NCC PI. Each Committee Chairman is provided with a contact list of members by the NCC. Terms for volunteers will be limited to three years. Potential advisors and ad hoc members will be appointed by the NCC MPIs.
B. Responsibilities: the WG clinical concept assessment responsibilities noted above will be managed by the WG chair or an appropriate delegate. Each task of the WG in the assessment process will be defined by the chairman and a timeline for completion provided. The Chairs are also responsible for providing the NCC with a yearly summary of activities, accomplishments, and goals for the coming year within stipulated time frames.
C. Meeting Frequency: the WG Chair is responsible for establishing virtual meetings on an as needed basis. Chairs or their designees are required to maintain attendance and written summaries or minutes for group calls. WG face to face meetings may occur in conjunction with StrokeNet meetings as needed.

5. Core Committees:

A. Training and Educational Cores - Implements StrokeNet-wide educational activities and mentoring programs. There are two training and education cores: The **Fellow Education and Training Core** and the **Clinical Research Professional (CRP) Training and Education Core**. The cores will work in collaboration with other networks.

1) Membership: NCC MPI appoints a Chair and Co-Chair, faculty, coordinators, Fellow-Trainees, Educational Coordinator and NINDS Project Scientist.
2) Responsibilities: Guidance for the network regarding expectations of Trainees. Implement educational resources/didactics, develop core curriculum of webinars, and develop ideas for innovation in stroke education.
3) Meeting Frequency: Virtual meetings will be scheduled monthly as needed. Face to face meetings may occur at other StrokeNet meetings. Chairman or delegates will maintain meeting minutes and attendance.

B. Diversity, Equity, and Inclusion Core – Develop and implement a detailed patient recruitment, retention, and community engagement plan, with attention to adequate racial and ethnic minority recruitment.

1) Membership: NCC MPI appoints a Chair and Co-Chair, faculty, Coordinators, Fellows-Trainees, Educational Coordinator and NINDS Project Scientist.
2) Meeting Frequency: Virtual meetings will be scheduled monthly as needed. Face to face meetings may occur at other StrokeNet meetings. Chairman or delegates will maintain meeting minutes and attendance.

6. Advisory Committees - Provide consultative expertise in areas needed to cover the spectrum of potential Clinical Stroke Trials. Standing Advisory Committees **include Patient Representative Advocacy, Pediatric Stroke, Preclinical Science, and Telestroke**.

A. Membership - Membership in these committees will be populated by investigators of the RCCs and recognized content experts.
B. Responsibilities- Content specific expertise, support, and feedback during the protocol review phase
C. Meeting Frequency- On an as needed basis

5. APPLICABLE REGULATIONS

6. REFERENCES TO OTHER APPLICABLE SOPs

7. ATTACHMENTS AND REFERENCES

8. **DOCUMENT HISTORY**

Version	Description of Modification Justification for Modification	Completion Date	Issue Date	Effective Date
1.0	Final	3-Jun-2014	3-Jun-2014	3-Jun-2014
2.0	Revision #1-clarification of WG term limits and process for change	6-Nov-2015	6-Nov-2015	6-Nov-2015
2.1	Biannual review with minor administrative changes	31-Oct-2016		
3.0	Final	19-Dec-2016	19-Dec-2016	19-Dec-2016
4.0	Review with current administrative changes	19-Feb-2023	19-Feb-2023	19-Feb-2023
5.0	NDMC minor edits to section B4	18-Aug-2023	18-Aug-2023	18-Aug-2023

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Version 5.0

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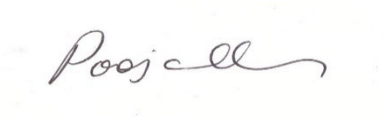
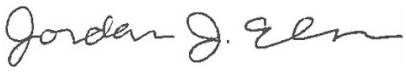
Reviewed and Approved by:



Pooja Khatri, MD, (StrokeNet NCC Principal Investigator)



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