SOP Number: ADM 25
SOP NAME: StrokeNet CIRB and DSMB Joint Operating Procedure
Effective Date: 15-Sep-2020 (rev 21-Apr-2023)

1. Policy

Human subject research regulations describing the roles of Institutional Review Boards (IRBs) in clinical trials research are found under the Common Rule, 45 CFR 46. The NIH also requires a Data and Safety Monitoring Board (DSMB) "for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an IRB".
While the roles and circumstances under which each entity functions and operates are stated in federal and NIH-wide guidelines, there is currently no available guidance as to how these two entities should interact. In addition, central IRBs are now often the IRB of record for all participating sites in a trial. We think that there is value in detailing how central IRBs and DSMBs interact. Both entities are required for many clinical trials, but the DSMB is an advisory body with full access, as needed, to trial data whereas a central IRB has authority to suspend all trial enrollment but without the same access to trial data. This document defines how these two bodies should interact within the StrokeNet framework.

The CIRB and the DSMB are both critical to the safe, ethical, and compliant conduct of StrokeNet clinical trials. The responsibilities of the DSMB and CIRB are unique but the scope of their oversight may overlap. The purpose of this Joint Operating Procedure (JOP) is to define the roles and interactions of the StrokeNet CIRB and DSMB during the approval and ongoing review of StrokeNet Clinical trials. This document provides guidance to harmonize and coordinate communications and expectations of the CIRB and DSMB to ensure the safety of participants in StrokeNet clinical trials, while maintaining the scientific integrity of the trials. It describes areas where the scope of review of these two bodies overlap, management of shared oversight, and communication strategies between these bodies.

Acknowledgment of these areas of overlap and coordination between the two bodies is intended to avoid confusion and optimize what could otherwise become discordant decisions and recommendations involving conduct of StrokeNet Clinical Trials.

2. Definitions and Abbreviations

Abbreviations:

CIRB	Central Institutional Review Board
CR	Continuing Review
DSMB	Data and Safety Monitoring Board
NDMC	National Data Coordinating Center at Medical University of South Carolina
NCC	National Coordinating Center at the University of Cincinnati

NINDS	National Institute of Neurological Disorders and Stroke
PPI	Protocol Principal Investigator
RCC	Regional Coordinating Centers

Definitions:

Central Institutional Review Board (CIRB): A single Institutional Review Board (IRB) that performs the required human subjects review under the Federal Policy for the Protection of Human Subjects and other applicable regulations as deemed necessary for multi-site clinical research.

Data Safety Monitoring Board (DSMB): An advisory committee of clinical research experts, such as physicians and statisticians, and patient advocates who monitor the progress of a clinical trial and review safety and efficacy data while the trial is ongoing. This committee is independent of the people, organizations, and institutions conducting the clinical trial. Data and Safety Monitoring Boards (DSMBs) can recommend that a trial be stopped early because of concerns about participant safety or because the main research question has been answered.

Protocol Principal Investigator (PPI): Investigator at the prime clinical trial award site who is responsible for development of the protocol and the coordination of the conduct of the clinical investigation at multiple sites, including required regulatory reporting to the CIRB. If this person is the IND or IDE holder, this individual is also responsible for all applicable FDA regulatory requirements, which includes all Sponsor-Investigator responsibilities.

3. Scope

The policies and procedures described in this SOP apply to parties involved with StrokeNet research, including the NCC, the CIRB, the NDMC and all StrokeNet RCCs and performance sites.

4. Procedures

A. DSMB Responsibilities

The DSMB is responsible for assuring to the NINDS that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards. The DSMB meets at specific intervals throughout the course of an ongoing trial to monitor accrued data on safety, efficacy or other pre-defined outcomes. An NINDS-appointed DSMB is required for trials which may modify the current standards of treatment or public health policy, result in the licensing of a therapeutic agent or device or extend approved indications to new groups of patients. A DSMB is mandatory for all Phase 3 clinical trials, and it may be required for some earlier phase trials (e.g., trials that involve multiple sites, pose significant risk to participants, are conducted in vulnerable populations, use certain controversial interventions).

B. CIRB Responsibilities

The CIRB oversees designated StrokeNet clinical trials at United States research sites (not conducted at VA sites) to protect the rights and welfare of participants in these trials. The CIRB must approve the StrokeNet clinical trials it oversees under Federal criteria for IRB approval of research 45 CFR 46.111 and, when applicable, 21 CFR 56.111. The CIRB has the authority to approve, require modifications (to secure approval), or disapprove research. The CIRB assures, both in advance and by periodic review that appropriate steps are taken to protect the rights and welfare of humans participating in the trials. Federal regulations require that the IRBs have the authority to suspend or terminate approved human subjects research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected and serious harm to subjects.

C. Shared Responsibilities

This process document identifies several areas in which the CIRB and the DSMB may have overlapping responsibilities and suggests the scope and focus of each body for each area, and which body might lead on each topic.

C.1 Protocol Review

The study protocol is reviewed by both the CIRB and the DSMB. Following approval of the study protocol by the CIRB, the DSMB should review the protocol prior to implementation. If revisions to the study protocol are required by the DSMB, a request for a protocol modification must be submitted to the CIRB.

C.2 Informed Consent Document (ICD) Review

Review of the ICD is the primary responsibility of the CIRB. However, the ICD will also be submitted to the DSMB with the study protocol, and they have the option to provide general comments and suggestions to the investigators to improve the document prior to submission with the CIRB application. Final wording of the ICD is proposed by the investigators and approved by the CIRB.

C.3 Review of New External Information

The Protocol Principal Investigator (PPI) of a StrokeNet clinical trial will promptly report any new external information that could affect the continued acceptability of the trial to the DSMB, CIRB, performance site investigators, the StrokeNet Steering Committee, and NINDS. When reporting such new external information, the PPI should also include an assessment of the impact of the external data on the trial, and an action plan if enrollment suspension, consent changes or protocol changes may be warranted.

C.3.1 DSMB Responsibilities

The DSMB should review new external information in the context of accumulating data in the present trial in a timely fashion. The DSMB will assess the continued ethical basis for continuation of the trial and may consider whether the external data obviates the value of the present trial, or if the present trial still represents important concordant or discordant data valuable to improving medical care of patients. When feasible, the DSMB might consider communicating directly with the DSMB responsible for overseeing the external data to gain greater insights than available from publicly available data.

C.3.2 CIRB Responsibilities

The CIRB will discuss the new external information during a convened meeting. If the CIRB determines the new information alters the IRB's previous conclusion that 1) the risks to subjects are minimized, and (2) the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result, the CIRB must take actions to address the concerns. The CIRB may determine that study activities and/or enrollment be suspended pending corrective actions being taken to address the concerns. If the CIRB determines that the concerns cannot be addressed, the study may need to be suspended to allow the DSMB time to conduct an interim analysis, as well as review any relevant external information, in order to provide its recommendations to NINDS and the CIRB.

Prior to the CIRB taking action, a conference call will be scheduled in an accelerated and timely fashion with the CIRB Chair and members, the PPI, NINDS and StrokeNet leadership, and the DSMB Chair and members to discuss potential actions that can be taken in response to the new information. A follow-up conference call will then take place to discuss the DSMB's recommendations. The CIRB will then meet to determine an appropriate action in response to the new information. Possible actions include but are not limited to:

- Suspension of research;
- Notification of current or past participants if such information will impact the participants' willingness to continue to take part in the research;
- Modification of the protocol and/or consent form;
- Requiring current participants to reconsent to participation;
- Modification of the CIRB's continuing review schedule;
- Monitoring of the research or monitoring of the consent process; or
- Referral to other organizational entities, as required.

C.4 Suspension or termination of a StrokeNet trial.
Recommendations or requirements to suspend a trial based on unexpected problems affecting risk to future participants, noncompliance, or multiple similar individual safety events are primarily the responsibility of the PPI and the CIRB. If the DSMB has concerns related to such events, these should be communicated to the CIRB.

Recommendations to suspend or terminate the trial based on assessments of relative efficacy and safety, or possible loss of equipoise, are primarily the responsibility of the DSMB. If the CIRB has concerns related to these issues, they should be communicated to the DSMB.

NINDS, as the granting institution, is ultimately responsible for decisions related to trial modification or termination.

D. Communications between the CIRB and DSMB
Communications of DSMB recommendations are described in the DSMB Charter. Per the charter, the DSMB communicates with the PPI and the Director of the NINDS Division of Clinical Research through the NINDS DSMB Liaison. Most often the actions and recommendations of either the DSMB or the CIRB can be communicated to each other through the PPI. In some situations, NINDS may also be involved in these communications.

When either the chairperson of the CIRB or the DSMB identify an issue for which direct communication between the bodies is desired, the chairpersons should communicate with the NINDS liaison officer directly who will set up a call with the three individuals. Communications between the CIRB and the DSMB would be expected to facilitate harmonized oversight decisions and recommendations in areas of overlapping responsibility.

8. Document History

Version	Description of Modification	Completion Date	Issue Date	Effective Date
1.0	Final	1-Sep-2020	TBD	Upon date of last signature
1.1	Removed sections 5-7	4-Sep-2020	15-Sep-2020	15-Sep-2020
2.0	Administrative review and minor edits	21-Apr-2023	27-Apr-2023	27-Apr-2023

NIH StrokeNet Network

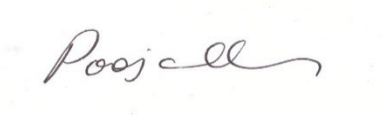
Standard Operating Procedure (SOP)

StrokeNet CIRB and DSMB Joint Operating Procedure

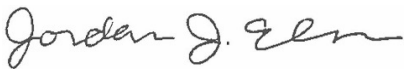
Version 1.1

ADM #25

Reviewed and Approved by:



Pooja Khatri, MD, (StrokeNet NCC Principal Investigator)



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