MANUAL OF PROCEDURES

Protocol Version / Version Date
Version 3.0; January 31, 2024

MOP Version
Version 2.0; March 5, 2024

Principal Investigators
Eva Mistry, MBBS, MSCI (Protocol PI); Pooja Khatri, MD, MSc (Contact PI)
Guy Reed, MD, MS; Jordan Elm, PhD

Supported by
The National Institute of Neurological
Disorders and Stroke (NINDS)

Translational Sciences, INC

IND Number: 122550
Protocol Number: TS23/DS9231-U202
NCT Identified Number: NCT05948566

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
2.0 Protocol Synopsis	Added SITS-MOST definition	Updated in protocol v 3.0
3.0 Study Schema	Changed ICPB to IVBP	Corrected typo
4.0 National Study Team Contact	Revised personnel	Personnel changes
6.2 Central IRB Essential Documents	Revised protocol signature and main ICF versions	Newer version is approved and available
10.1 Inclusion Criteria	Added image to show image acquisition time and clarify which time to use for study drug start time	Clarify which imaging time should be used
10.1 Inclusion Criteria	Revised PTT to aPTT	Revised to be consistent with protocol revisions
14.0 Laboratory Studies	Added section 14.0	Provide clarification regarding SOC and research labs
15.0 and on	Revised numbering to reflect added section	Added section required renumbering
17.0 Study Visits and Assessments	Revised Schedule of Activates	Revised to be consistent with protocol revisions
17.1 Baseline	Clarifying language regarding laboratory evaluations	Provide additional clarification
17.2 Study Drug Administration	Clarifying language regarding laboratory evaluations	Provide additional clarification
17.3 Post Study Drug	Clarifying language regarding laboratory evaluations	Provide additional clarification
17.430 (±4) Hour Visit-Primary Outcomes Visit	Clarifying language regarding laboratory evaluations	Provide additional clarification
18.3.2 Relationship to Study Intervention	Update definitions to reflect those listed in WebDCU	Ensure consistent language
Appendix 1	Added instructions for randomization with pictures	Provide detailed instructions for randomization

Contents

1.0 List of Abbreviations and Definitions

Abbreviation	Term/ Definition
a2-AP	alpha-2 antiplasmin
AE	Adverse Event
AESP	Adverse Event Special Interest
CBC	Complete Blood Count
CCC	Clinical Coordinating Center
CDA	Confidential Disclosure Agreement
cIRB	Central Institutional Review Board
CONSORT	Consolidated Standards of Reporting Trials
CPS	Clinical Performance Site
CRF	Case Report Form
CRNM	Clinically relevant non-major
CTA	Clinical Trial Agreement
CTMS	Clinical Trial Management System
DCR	Data Clarification Request
DM	Data managers
DOA	Delegation of Authority
DSMB	Data Safety Monitoring Board
EC	Executive Committee
eICD	Electronic Informed Consent Document
EIU	Exposure In Utero
fCOI	Financial conflict of interest
GCP	Good clinical practice
ICD	Informed Consent Document
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IMC	Imaging Management Center
IMM	Independent Medical Monitor
IND	Investigational New Drug
IP	Investigational Product
LAR	Legally Authorized Representative
LKW	Last known well
LP	Lab Personnel
mITT	modified Intent-to-Treat
MMP-9	Matrix Metalloproteinase-9
MOP	Manual of Procedures
MPI	Multiple Principal Investigators
mRS	Modified Rankin Scale
NCC	National Coordinating Center
NDMC	National Data Management Center
NIHSS	NIH Stroke Scale
OTC	Over the counter
PD	Protocol Deviation
Ph	Pharmacy staff
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PM	Project Manager

PPh	Primary Pharmacist
PSC	Primary Study Coordinator
PUD	Public use dataset
RCC	Regional Coordinating Center
RCL	Reed Central Laboratory
RDC	Regulatory Document Coordinator
RNI	Research New Information
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SISTER	Strategy for Improving Stroke TrEatment Response
SOC	Standard of Care
SSC	Secondary Study Coordinator
SSC	Secondary Study Coordinator
SSL	Secure Sockets Layer
Sub-I	Sub-Investigator
TS23	Study drug
UC	University of Cincinnati
UE	Unanticipated Event

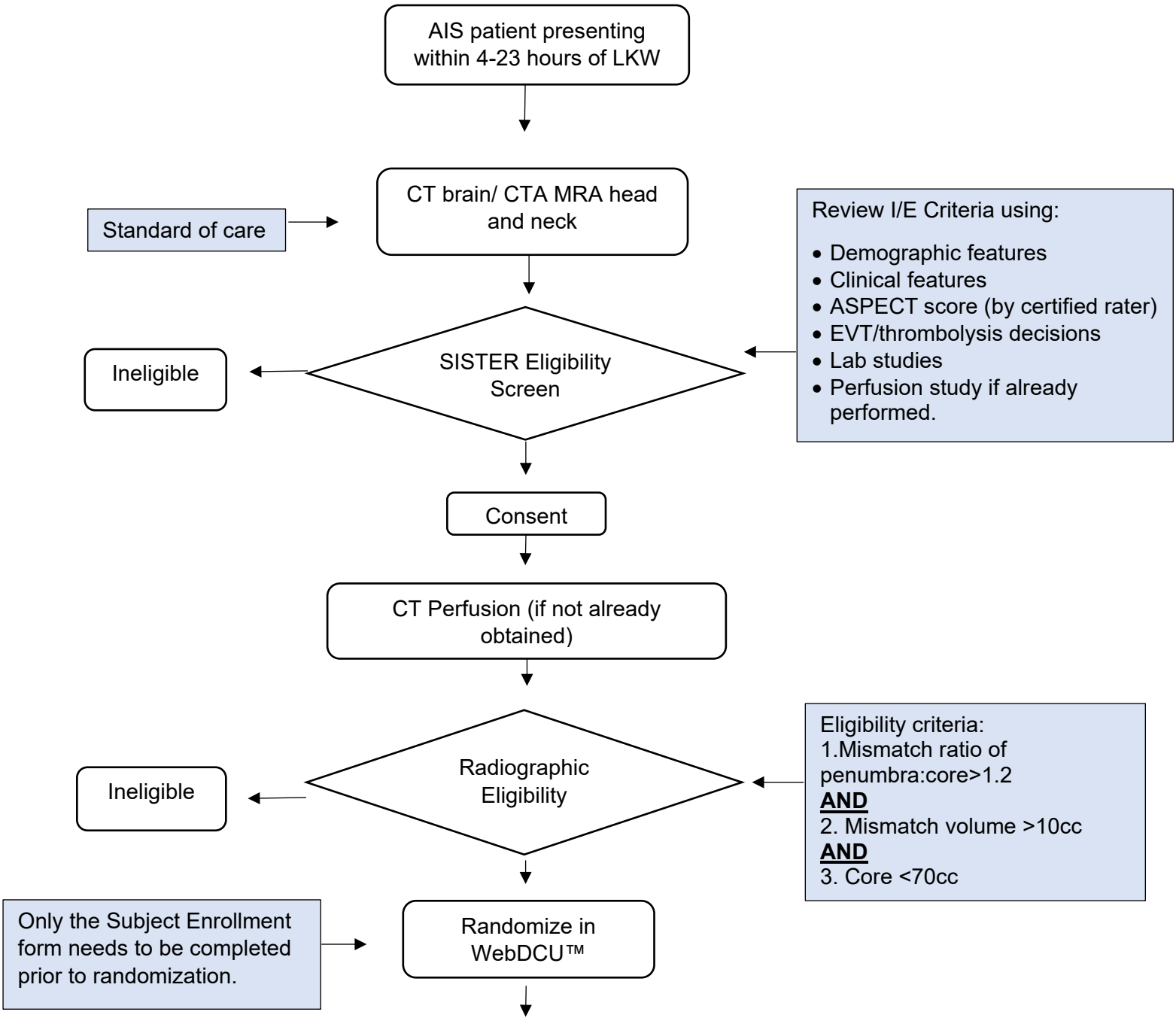
2.0 Protocol Synopsis

Title:	Strategy for Improving Stroke TrEatment Response (SISTER)
Study Description:	*SISTER is a Phase-2, prospective, randomized, placebo-controlled, blinded, dose finding trial that aims to determine the safety and preliminary efficacy of TS23, a monoclonal antibody against the alpha-2 antiplasmin (a2-AP), in acute ischemic stroke.*
Objectives:	Primary Objective: To identify a dose of TS23 that is safe and more efficacious than placebo for the treatment of patients from 4.5 to 24 hours of ischemic stroke onset (or last known well), who have evidence of core-penumbra mismatch on perfusion imaging and are not a candidate for standard of care reperfusion therapies.
Endpoints:	**Primary Endpoints:** 1. Safety: ANY intracranial hemorrhage (ICH) visualized on the CT scan 30 (±4) h after study drug administration. 2. Efficacy: NIH Stroke Scale Score at 30 (±4) h after study drug administration (adjusted for the baseline in analysis) **Secondary Endpoints:** Biomarker Efficacy: 1. a2AP activity at 3 (±1) h after completion of therapy 2. Matrix metalloproteinase-9 (MMP-9) plasma level 3 (±1) h after completion of therapy. 3. % tissue reperfusion on 30 (±4) h perfusion scan compared to the baseline Clinical Efficacy**:** 1. Improvement in level of global disability (Modified Rankin Scale (mRS) distribution) at 90 (±7) days. 2. Frequency of excellent functional outcome (mRS 0-1) at 90 (±7) days. 3. National Institutes of Health Stroke Scale (NIHSS) at 72 (±12) h (or discharge if sooner; adjusted for the baseline in analysis) Pharmacokinetics and anti-drug antibodies: 1. Pharmacokinetic (PK) profile of TS23 at 3 (+/-1) h and 30 (±4) h after completion of therapy and 90 (±7) days. 2. Evaluation of anti-drug antibodies to TS23 (at baseline and 90 (±7) d follow-up visit).

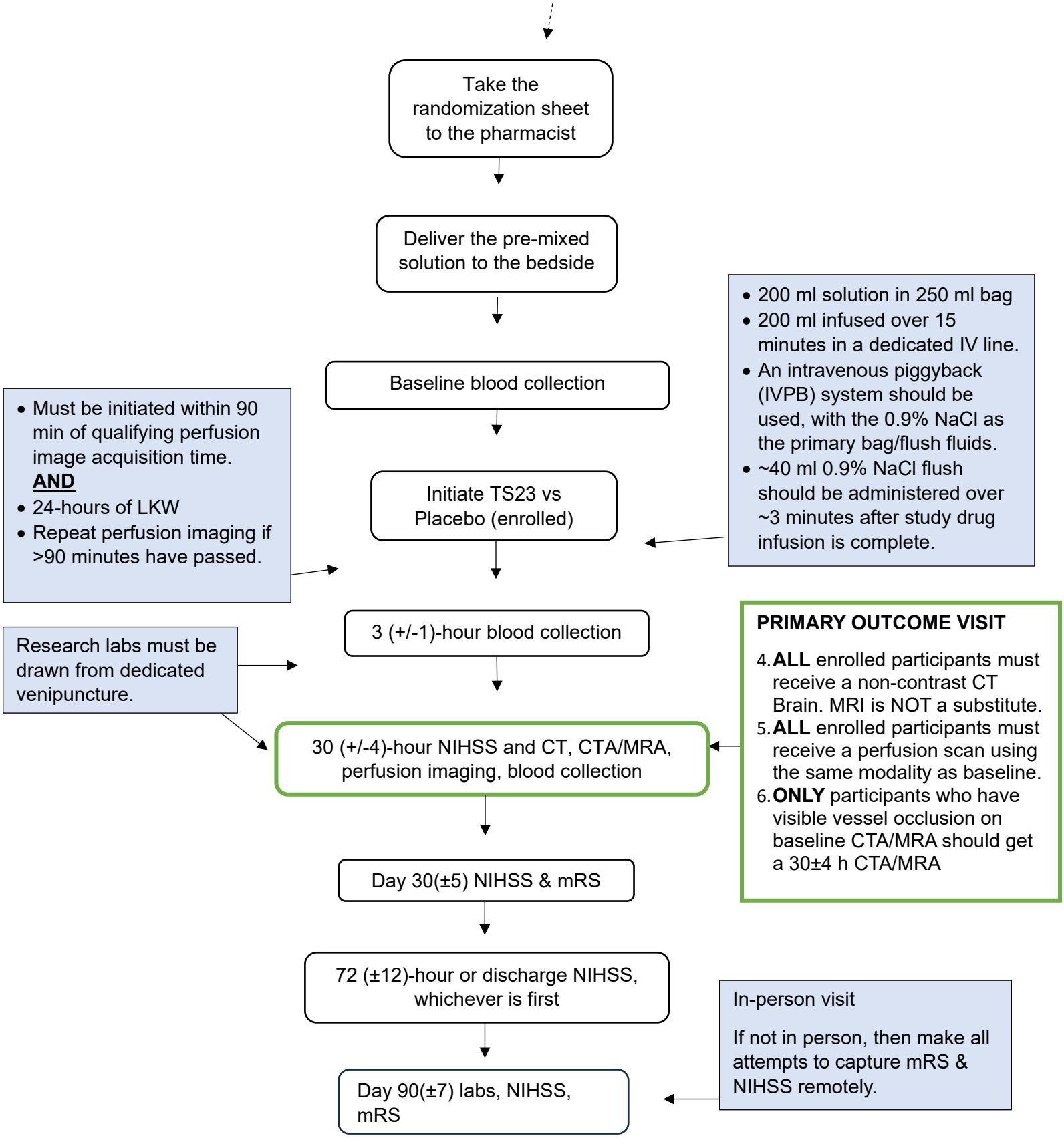
	Safety: 3. Incidence of symptomatic ICH within 30 (±4) h of study drug administration [(SITS-MOST definition) (a local or remote type II parenchymal hemorrhage within 30 (±4) h after treatment associated with a ≥ 4-point deterioration on the NIHSS score from baseline or from the lowest score from baseline to 24 hours, or leading to death.)] 4. Incidence of non-ICH major or clinically relevant non-major bleeding within 30 days of study drug administration. 5. Non-bleeding, serious adverse events (SAEs) within 90 (±7) days 6. Incidence of stroke-related and all-cause deaths within 90 (±7) days 7. Plasma fibrinogen levels at 3 (+/-1) h after completion of study drug administration
Study Population:	We will enroll a total of 300 adults (≥18 years) with acute ischemic stroke who have a baseline NIHSS ≥6 and are able to receive study drug within 4.5-24 hours after stroke onset (or last known well) who have evidence of core-penumbra mismatch on baseline perfusion imaging and are not planned for endovascular intervention or standard of care intravenous (IV) thrombolysis.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Consecutive eligible patients will be screened and enrolled in up to 50 comprehensive stroke centers in the U.S. Currently, no sites outside of the U.S. are planned.
Description of Study Intervention:	The study intervention arms are TS23 (dosed at 3, 5, 7, or 10 mg/kg) or matching placebo. Study drug is administered intravenously as short IV infusion after reconstitution over ~15 minutes (max dose of 1000 mg).
Study Duration:	54 months
Participant Duration:	3 months

3.0 Study Schema

The study schema with notes is split between the next two pages. The first covers through randomization and the second, covers deliver of the study drug to bedside through the 90 (±7) day visit.



(continued…)


Take the randomization sheet to the pharmacist
Deliver the pre-mixed solution to the bedside
Baseline blood collection
Initiate TS23 vs Placebo (enrolled)
3 (+/-1)-hour blood collection
30 (+/-4)-hour NIHSS and CT, CTA/MRA, perfusion imaging, blood collection
Day 30(±5) NIHSS & mRS
72 (±12)-hour or discharge NIHSS, whichever is first
Day 90(±7) labs, NIHSS, mRS
• 200 ml solution in 250 ml bag
• 200 ml infused over 15 minutes in a dedicated IV line.
• An intravenous piggyback (IVPB) system should be used, with the 0.9% NaCl as the primary bag/flush fluids.
• ~40 ml 0.9% NaCl flush should be administered over ~3 minutes after study drug infusion is complete.
• Must be initiated within 90 min of qualifying perfusion image acquisition time.
AND
• 24-hours of LKW
• Repeat perfusion imaging if >90 minutes have passed.
Research labs must be drawn from dedicated venipuncture.
PRIMARY OUTCOME VISIT
4. ALL enrolled participants must receive a non-contrast CT Brain. MRI is NOT a substitute.
5. ALL enrolled participants must receive a perfusion scan using the same modality as baseline.
6. ONLY participants who have visible vessel occlusion on baseline CTA/MRA should get a 30±4 h CTA/MRA
In-person visit
If not in person, then make all attempts to capture mRS & NIHSS remotely.

4.0 National Study Team Contact List

URGENT Trial Assistance

24/7 SISTER Trial Hotline: 1-866-212-7187
Questions requiring **immediate assistance** regarding eligibility, protocol implementation, or safety questions.

WebDCU™ Emergency Randomization Hotline: 1-866-450-2016
***Call for randomization difficulties ***

SISTER Primary Study Contact List			
Title and Responsibility	**Name**	**Contact Information**	**When to Contact**
Principal/ Protocol Investigator	Eva A. Mistry, MBBS, MSCI	mistryea@ucmail.uc.edu 513-558-1291	Protocol inclusion/exclusion questions, medical management treatment and any SAEs or unanticipated problems.
Principal/ Contact Investigator	Pooja Khatri, MD, MSC	Pooja.khatri@uc.edu	Protocol inclusion/exclusion questions, medical management treatment and any SAEs or unanticipated problems.
Principal Investigator Biostatistician	Jordan Elm, PhD	elmj@musc.edu	Please route all questions to Protocol or Contact PI
Principal Investigator	Guy Reed, MD, MS	guyreed@arizona.edu	Please route all questions to Protocol or Contact PI
NCC Project Manager	Pam Plummer, MSN, RN, CCRC	plummepa@ucmail.uc.edu 513-885-2437	Study related clinical or trial operations questions, regulatory and cIRB submissions, site payments.
WebDCU™ Data Manager	Katie Stever, MPH	steverca@musc.edu 843-792-2077	Study related data management questions.
WebDCU™ Data Manager	Riley Luckmann	luckmann@musc.edu	Study related data management questions.
Site Monitoring Manager	Aaron Perlmutter, MPH, MSW	perlmutt@musc.edu 843-792-2784	Study related monitoring management questions.

StrokeNet National Coordinating Center Contact List			
Title and Responsibility	**Name**	**Contact Information**	**When to Contact**
NCC CIRB Liaison	Susan Roll, RN, BSN, CCRP	rollsn@ucmail.uc.edu 513-558-6061	Direct questions to NCC PM
NCC Regulatory Compliance Specialist	Kimberly Lever, MA	leverky@ucmail.uc.edu	Questions about *initial* cIRB submission and cIRB modifications
NCC Contract Specialist	Sasha Simms	sinclapl@ucmail.uc.edu	Questions regarding clinical trial agreements (CTA).
NCC Financial Specialist	Paula Sinclair	sinclapl@ucmail.uc.edu	Per-subject payment questions

StrokeNet National Coordinating Center Central Pharmacy			
Title and Responsibility	**Name**	**Contact Information**	**When to Contact**
StrokeNet Pharmacist	Noor Sabagha RPh, MPH	SISTERtrialRX@ucmail.uc.edu 513-584-3166	Pharmaceutical questions/issues
StrokeNet Pharmacist	Chris Unger, PharmD	SISTERtrialRX@ucmail.uc.edu 513-584-3166	Pharmaceutical questions/issues
Pharmacy Technician	Brittany Dornheggen	SISTERtrialRX@ucmail.uc.edu 513-584-3166	Study drug supply or shipments, changes in shipping information
Pharmacy Technician	Carla Jones	SISTERtrialRX@ucmail.uc.edu 513-584-3166	Study drug supply or shipments, changes in shipping pharmaceutical information

Translational Sciences, Inc- Central Lab			
Title and Responsibility	**Name**	**Contact Information**	**When to Contact**
Professor	Inna Gladysheva, PhD	innagladysheva@arizona.edu 602-827-2919	Route questions to Clinical Project Manager
Senior Research Scientist	Joseph S.Y. Jeong, PhD	sunyongj@translationalsciences.com 919-282-7718	Plasma sample shipping and receiving.
Senior Scientist & Clinical Project Manager	Ryan Sullivan, DVM, RLATG	rsullivan@translationalsciences.com 352-213-1045	Logistics, kit inventory, shipping concerns, and general questions.

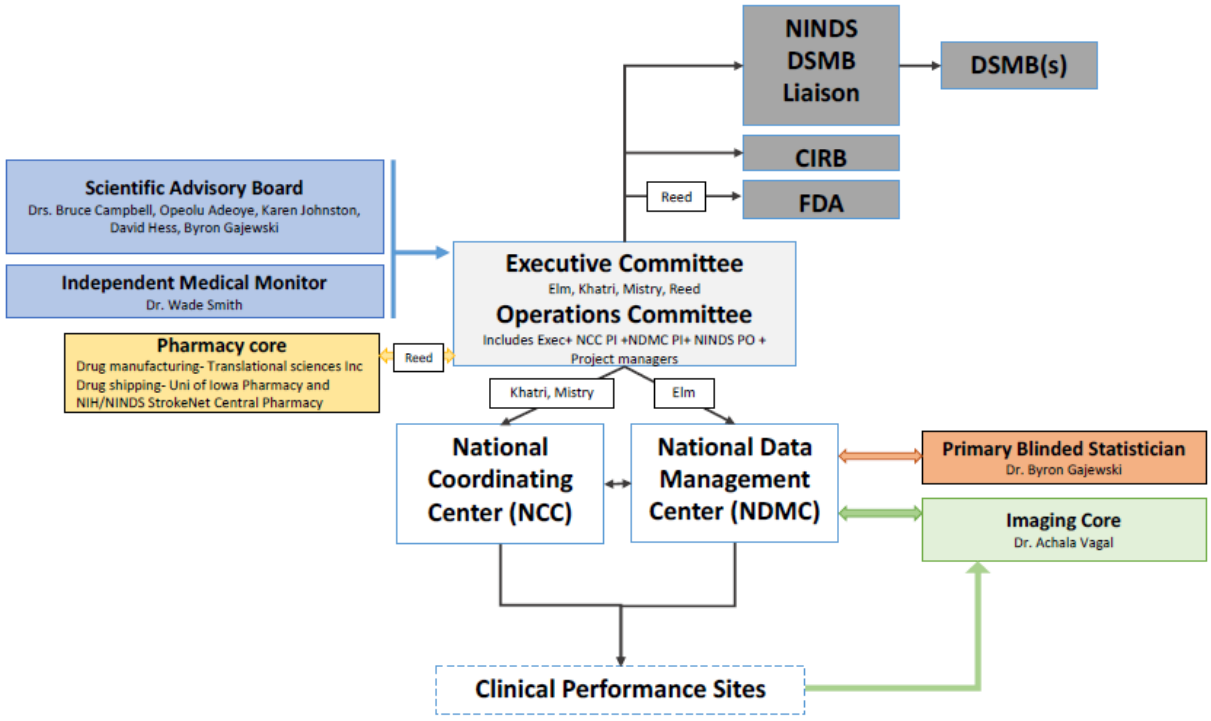
Imaging Management Center at University of Cincinnati			
Title and Responsibility	**Name**	**Contact Information**	**When to Contact**
Research Manager	Vivek Khandwala, PhD	khandwvj@ucmail.uc.edu 513-558-2044	Route question to Project Manager
SISTER Imaging Project Manager	Holly Wilcox	wilcoxhy@ucmail.uc.edu 513-558-3883	Primary contact for any imaging related questions/concerns.

RAPID AI			
Title and Responsibility	**Name**	**Contact Information**	**When to Contact**
Sr. Clinical Affairs Manager	Natalie Zaba	zaba@rapidAI.com 440-264-3145	Any RAPID trial related questions
24/7 RAPID AI Technical/ Software Support **1-833-RAPIDAI (833-727-4324)** support@rapidai.com			

National Institute of Neurological Disorders and Stroke- SISTER Officials		
Title and Responsibility	**Name**	**Contact Information**
NINDS Program Scientist	Scott Janis, PhD	janiss@ninds.nih.gov
NINDS Program Official	Mariam Afzal, B.A.	mariam.afzal@mail.nih.gov
NINDS Program Official	Laura Kimberly, BS, CIP	Laura.kimberly@nih.gov

5.0 Study Organization, Roles, and Responsibilities

5.1 Organizational Chart



5.2 StrokeNet National Coordinating Center

The NIH has created the NIH StrokeNet National Coordinating Center (NCC) to conduct small and large clinical trials and research studies to advance acute stroke treatment, stroke prevention, and recovery and rehabilitation following stroke. In addition, NIH StrokeNet provides an educational platform for stroke physicians and clinical trial coordinators. The NCC is responsible for the network infrastructure, initiation of collaborative relationships, facilitation of the study design, oversight, and management of network studies. Operationally, the NCC is the home for the Central Institutional Review Board (CIRB) for the NIH StrokeNet. The NCC works with the protocol Principal Investigator(s) (PI) and his/her/their team to manage trials within the NIH StrokeNet.

SISTER study specific information is posted on the NIH StrokeNet website with information for study personnel, patients, and other interested parties.

The StrokeNet NCC Co- Principal Investigator, Dr. Joseph Broderick will lead the primary elements of study operations conducted through the NCC at the University of Cincinnati. Dr. Broderick will be assisted by a NCC Project Manager, Pam Plummer MSN, RN, CCRC, Contract Specialist, Regulatory Compliance Specialist, and Financial Administrative Staff.

Specific Functions of the NCC include:

- Coordinate efforts with the Protocol PI, Prime Project Manager, and NDMC
- Ensure all site agreements are fully executed.
- Assist confirming and/or establishing Reliance Agreements (as necessary)
- Facilitate CIRB submissions and approvals.

- Central management of electronic consent
- Review and process regulatory documents
- Ensure regulatory compliance.
- Notify NDMC when sites are ready to be released to enroll.
- Track recruitment and site performance
- Manage and process start-up and per-subject site payments.
- Review and manage safety reporting and provide reports to drug companies, as required.

***5.2.1 NCC Project Manager*:** will coordinate with the Multiple Principal Investigators (MPIs) and Prime Project Manager (PM) as well as the CIRB and National Data Management Center (NDMC). She collaborates with the Prime PM to manage tasks related to clinical performance sites and site start-up activities, provides regulatory review via WebDCU™ for all study staff credentials; reviews CIRB submission materials and continuing review documents from sites; assists site with submissions to CIRB for review and approval; performs initial review of acuity and completeness of reported safety events requiring Independent Medical Safety Monitor review; verifies contractual and regulatory requirements prior to site authorization to begin active recruitment; and verifies subject payments with NCC financial manager.

***5.2.2 NCC Contract Specialist*:** prepares and executes the SISTER Clinical Trial Agreement (CTA) for both network and non-network performance sites. The CTA contains a fixed cost per subject payment budget, a special NINDS approved F&A rate, a Standard of Care document and any special terms and conditions associated with trial recruitment and payment.

***5.2.3 NCC Grants and Financial Specialist*:** initiates subject enrollment invoices. Participating clinical performance sites will not be required to submit invoices to their Regional Coordinating Center (RCC) or the NCC for any completed study related activities. Per subject payments will be identified by completed data entry and using the NDMC WebDCU™ payment module. Payments for subject enrollment and other interval payments as outlined in the CTA will be determined automatically at least monthly for all milestones and tasks completed and confirmed by the NDMC.

5.2.4 StrokeNet Central Institutional Review Board (CIRB): located at the University of Cincinnati (UC) is the trial protocol CIRB of record for all participating sites following execution of a Reliance Agreement with sites outside the network.

5.2.5 NCC CIRB Liaison: works with the trial specific Project Managers, Coordinators at participating sites and WebDCU™ on regulatory document compliance, developing and approving informed consent documents, HIPAA authorization, HIPAA waiver for screening if applicable, protocol amendments, unanticipated event reports, approval of recruitment materials, and annual and continuing review.

Trial specific information will be posted prominently on the www.NIHStrokeNet.org website with information for study personnel, interested clinicians, patients, and other interested parties.

5.3 Clinical Coordinating Center

The Protocol Principal Investigator, Dr. Eva Mistry, directs the activities of the Clinical Coordinating Center (CCC) with Dr. Pooja Khatri, who is the Contact Principal Investigator. She is assisted by the Prime Project Manager, Sarah Bailey, MS.
Specific functions of the CCC include:

- Oversee the clinical aspects of the trial.
- Conduct investigator and coordinator training.
- Conduct site readiness calls.

- Ensure site adherence to the protocol.
- Monitor site enrollment and performance.
- Ensure recruitment goals are met.
- Ensure all data, images, and specimens are submitted.
- Coordinate interactions between CCC, NCC, and NDMC
- Liaison with NINDS and Translational Sciences, Inc.

5.3.1 Protocol Principal Investigator: oversees trial and site startup, the protocol, its amendments, and its implementation. She works in close conjunction with the Prime and NCC PM and Dr. Khatri to develop the Manual of Operations for Policies and Procedures (MOPP), and the start-up and training of the clinical performance sites. She will be responsible for periodic site-retraining, addressing protocol deviations and troubleshooting recruitment issues. She works closely with the NIH StrokeNet pharmacy, Translational Sciences, imaging core, NCC, and NDMC to ensure efficient trial operations. She also has supervisory responsibility over the overall Project Manager of the SISTER trial.

5.3.2 Contact Principal Investigator*:* oversees the administrative aspects of the grant. She keeps all components of the trial led by the individual MPIs working well together, including the trial's protocol, pharmacy, and statistical activities, and the NIH StrokeNet infrastructure, including its National Coordinating Center (NCC), Data Management and Statistical Center (NDMC), and central pharmacy and imaging cores.

5.3.3 Prime Project Manager*:* coordinates with the NCC PM as well as the CIRB and NDMC. Acts as the primary point person for all Data and Safety Monitoring Board (DSMB) correspondence, sends trial updates and urgent notifications to sites, maintains ongoing communication between University of Cincinnati CCC, NCC and NDMC, documents and manages site training at participating CPSs, and coordinates communication on behalf of the trial. Assists the Protocol and Contact PI with preparation, submission and maintaining reports and correspondence.

5.3.4 Internal Medical Monitor: Dr. Yasmin Aziz serves as the Internal Medical Monitor for SISTER. She assists Dr. Mistry and the National Data Management Center in preparing blinded safety reports for review by the Independent Medical Monitor.

5.4 StrokeNet National Data Management Center at the Medical University of South Carolina (MUSC)

The National Data Management Center (NDMC) is located in the Data Coordination Unit housed within the Department of Public Health Sciences at the Medical University of South Carolina. The NDMC provides the following support for the trial:

- **Data Management**: Digitalization of the protocol, development of Case Report Forms, data quality assurance, site monitoring, and database technical support.
- **Statistical**: unblinded statistical analysis, development of study protocol, development and implementation of randomization plan, generation of reports, validation of primary analysis, participation in writing of manuscripts, and preparation of public use data set.
- Prepares DSMB reports.
- **IS/IT**: Clinical Trial Management System (CTMS) development, data transfer, system integration, and system infrastructure support.

- Complies with regulatory requirements and guidelines, including Code of Federal Regulations Title 21, HIPAA, ICH guidelines, and a complete set of internal SOPs for trial management.
- During the trial operation period, data managers (DMs) and monitors oversee the quality and efficiency of trial conduct and clinical data collection across all clinical sites and provide instructions and technical support for WebDCU™ users.

5.5 StrokeNet NCC Central Pharmacy

The NIH StrokeNet Central Pharmacy, located at the University of Cincinnati, will be the Central Pharmacy (CP) for SISTER. The central pharmacy will be responsible for supplying the participating sites with the IP. The central pharmacy will maintain logs of the kits provided to each site, recalling products that are due to expire, re-supplying sites with the investigation product as necessary, and interacting with Translational Science, Inc. The WebDCU™ system will be used for pharmacy management and drug supply communication with sites.

5.5.1 NCC Central Pharmacist

The StrokeNet Central Pharmacist serves as a Clinical Research Administrator and Director who will be responsible for all aspects of investigational product management and distribution for all drug studies within the StrokeNet.

The Central Pharmacist meets the following Qualifications and Pre-requisites:

- Ohio License from State Board of Pharmacy
- RPh or PharmD
- Previous experience with investigational drug management preferred but not required.
- Ability to Obtain Independent Pharmacy Licensure from State Board of Pharmacy
- Eligibility to apply for an institutional DEA license.
- Eligibility to apply for a wholesale license.

5.5.2 NCC Pharmacy Technician: Works directly under the supervision of the NCC Central Pharmacist preparing and dispensing investigational drug for the SISTER trial. Manages required record-keeping, shipping, ordering, and inventory activities. Ensures the accuracy and integrity of products prior to their delivery to study sites. Ensures compliance with all applicable, governmental, and sponsor regulations, laws and policies related to the conduct of trials involving investigational or marketed drugs. Maintains records to meet sponsor requirements, FDA regulations and legal requirements for pharmacy operations.

5.6 Imaging Management Center (IMC) at the University of Cincinnati

The University of Cincinnati Imaging Management Center (IMC) will be assisting participating sites in the timely collection and processing of DICOM imaging data on behalf of the SISTER Trial via the secure Ambra Health® web-based imaging management platform.

5.7 Central Laboratory- Translational Sciences, Inc.

Translational Sciences, Inc. has a central laboratory located on the Phoenix Biomedical Campus in Phoenix, Arizona – REED CENTRAL LABORATORY (RCL). All designated central laboratory plasma samples will be collected from the individual Clinical Performance Sites (CPSs) and shipped or transferred to the central lab for further processing according to site specific frequency schedule.

Please refer to the Lab MOP for full details regarding lab kits, specimen collection, collection schedule, specimen processing, etc.

5.8 Leadership Committees and Study Cores

5.8.1 SISTER Executive Committee (EC): The leadership structure involves non-overlapping, complementary roles for the multiple-principal investigators: Drs. Pooja Khatri, Jordan Elm, Eva Mistry, and Guy Reed. As the executive committee, they oversee all study operations (in conjunction with the Operations Committee) and interact with the Central Institutional Review Board (cIRB) and Data Safety and Monitoring board (DSMB). The executive committee will also regularly interact with the FDA and the primary contact is Dr. Reed, who is also the primary Investigational New Drug (IND) holder.

5.8.2 Operations Committee: The Operations Committee consists of key study investigators and personnel, including NINDS program officer, the PIs of the National Clinical Coordinating Center (NCC) and National Data Management Center (NDMC), and the NCC and Prime project managers. The Operations committee has the overall responsibility for the direction of the study.

The committee convenes weekly to oversee and review the progress of the study, discuss, and recommend to the EC any major changes in study procedures or direction, reviews protocol adherence, and data collection and analyses.

5.8.3 Publication Committee: The publication committee for SISTER includes the Operations committee, Scientific Advisory Board, and PIs of the three highest enrolling sites. This committee ensures robust dissemination of results and equitable authorship opportunities for all stakeholders. The committee is charged with finalizing a publication policy prior to trial launch which will be communicated to all study investigators and adherent to the StrokeNet Publication Policy standard operating procedures.

5.8.4 Scientific Advisory Board (SAB): The scientific advisory board convenes on a biannual basis to advise the MPIs on various aspects of study design and conduct. They provide advice regarding recruitment and retention issues, inclusion/exclusion criteria, protocol adherence, endpoint evaluations, statistical analysis, reporting of study results, and future trial design considerations.

5.8.5 Imaging Core: The neuroimaging repository for SISTER is housed at the University of Cincinnati under the leadership of Dr. Achala Vagal. The imaging core is responsible for imaging data collection, quality assurance/quality control, and storage of study imaging data. In addition, they are responsible for coordinating central image review by the blinded neuroimaging readers. They work closely with Dr. Elm and the study Project Managers to ensure that blinded imaging case report forms are linked to the overall study case report forms.

5.8.6 Pharmacy Core: Translational Sciences Inc. has and will manufacture TS23 according to GMP. The manufactured drug is shipped to the University of Iowa pharmacy for packaging and labeling. Packaged and labeled drug is then shipped to the StrokeNet Central pharmacy located at the University of Cincinnati for shipping to the individual sites.

5.8.7 Data and Safety Monitoring Board: This independent committee performs data reviews and analyses at regularly scheduled intervals and is responsible for final determinations of safety and ethical concerns, recommendations about whether the study should continue, and other related issues. The DSMB has access to the Independent Medical Safety Monitor who reviews adverse events on an ongoing basis. The members of the DSMB have been chosen by the program staff at NINDS and do not include any of the PIs or members of the study team.

The DSMB will review data quality and completeness, monitor fidelity to the study protocol, review the adequacy of participant recruitment and retention, review SAEs, and AEs of special interest and make recommendations to the NINDS and the study co-PIs concerning trial continuation, modification, or conclusion.

The DSMB may recommend modifications to the protocol if a reversible safety issue is identified. After each meeting, the liaison to the DSMB will prepare a letter to the study principal investigators, which will summarize the DSMB recommendations following the safety review. This letter will be provided to the CIRB and site investigators.

5.8.8 Independent Medical Monitor (IMM): Dr. Wade Smith serves as the blinded independent medical monitor and will review adverse events and serious adverse events, including the review of clinical history, neuroimaging reports, and any other data related to the safety event. He will communicate significant findings to the executive committee, the NDMC, and the DSMB as appropriate. The IMM will conduct a review of each SAE to determine expectedness. If the IMM determines the event to be serious, unexpected, and study related, the event will be reported promptly to the CIRB and other IRB/REBs with study oversight according to CIRB and local regulations via a Safety Report generated in WebDCU™.

5.9 Clinical Performing Sites (CPS)

Up to fifty clinical performing sites will be participating in the SISTER study. StrokeNet CPS selection is based on feasibility surveys and factored in the number of strokes reported, number of competing trials, clinical trial experience, and diversity of patient population. It is an expectation that Investigators and CPSs agree to follow FDA regulations outlined in 21 CFR Part 812, Protection of Human Subjects; and 21 CRF Part 54, Financial Disclosure by Clinical Investigators.

Study leadership at participating CPSs is comprised of one Site PI who is responsible for the overall conduct and performance at their site. A Primary Study Coordinator (PSC) and Primary Pharmacist (PPh) are also required roles. In addition, SISTER study team members may include sub-investigator(s), study coordinators, additional pharmacists, regulatory specialists and other qualified study staff who will be responsible for enrolling the participants and collecting the data for this trial.

Each CPS is expected to comply with all terms and conditions listed in the SISTER CTA. Each site will be responsible for uploading all applicable regulatory documents deemed necessary by the NCC for the initiation of this trial protocol into WebDCU™ as outlined in the Regulatory Document Parameters for WebDCU™ located in WebDCU™ under Project Documents. All sites are expected to comply with state and federal requirements for the initiation and ongoing performance of a clinical trial and adherence to the CIRB requirements for obtaining subject consent and reporting of protocol defined SAEs and unexpected events. Sites will identify and recruit appropriate study candidates as defined by the trial's inclusion and exclusion criteria.

If a site has a change in study staff, the new individual will be required to complete all applicable training. The site should alert both the Prime and NCC PMs to any upcoming changes in the coordinator coverage of the trial in a timely manner. New personnel joining the trial, must complete the pertinent on-line training via the WebDCU™ training site https://webdcu.musc.edu/campus/ prior to participating in any study related activities.

5.9.1 Site Principal Investigator

The Site PI is responsible for personally conducting and supervising the study. S/he/they can delegate certain study-related tasks to individuals who are qualified by training, education, and experience to perform the task; however, the Site PI never relinquishes responsibility for those

tasks and their outcomes. All delegated tasks must be detailed on the Delegation of Authority (DOA) Log.

In the case the site wishes to change their site PI, the potential PI must be reviewed by the Protocol and Contact PIs and accepted. When accepted, specific forms must be completed, and site-specific documents need to be amended. These documents must be approved by the cIRB prior to the new PI working on the study. All training must also be completed prior to working on the study.

Screening and Publicity

- Screen eligible subjects for the trial
- Generate enthusiasm for the trial at the site (e.g., with residents, fellows, and other faculty)
- Develop an effective system for screening and recruiting subjects with the help of the coordinator.
- Ensure subjects meet all inclusion and no exclusion criteria for enrollment.

Enrolling and Following Subjects

- Conduct or delegate the responsibility to conduct the neurological exam at enrollment and as required during follow-up.
- Assist the coordinator in uploading the protocol-required images to the online portal of the Imaging Management Center at UC
- Assist the coordinator with completion of clinical baseline and follow-up CRF worksheets and sign relevant source documents.
- Ensure adherence to the study protocol by all site study personnel.
- Monitor and respond to any adverse events as outlined in the protocol.

Potential End Point or Adverse Event Review

- Determine if an endpoint or adverse event has occurred.

Communication with Clinical and Statistical Coordinating Centers

- Maintain an open line of communication with local and national study staff.
- Attend investigator meetings and study webinars.
- Communicate leadership and regulatory bodies regarding adverse and unanticipated events as outlined in the protocol.

5.9.2 Primary Study Coordinator (PSC)

Screening

- Screen eligible subjects for the trial
- Generate enthusiasm for trial at the site and assist with trial specific educational efforts for the site and study personnel.
- Collaborate with PI to develop an effective system for recruiting and retaining subjects.

Enrollment of a Subject and Follow-Up

- Ensure the current cIRB approved consent form is signed before subjects are enrolled.
- Initiate randomization by entering the required data into WebDCU™
- Ask the subject to identify at least two contacts who could be reached if the subject is lost to follow-up.

- Ensure copies of all baseline and follow up CT, MRI, CTA, MRA, CT/MR perfusion imaging, and/or DSA films are uploaded to Ambra.
- Maintain a log of scheduled follow up evaluations for each study subject.
- Ensure that all data forms are completed and entered in WebDCU™ within 5 working days.
- Respond to all data clarification requests (DCRs) within 5 working days of query generation, except those associated with SAEs, which must be answered within 24 hours, excluding holidays/weekends, of query generation.
- Maintain site IRB approval for the study site.
- Maintain all essential study documents.
    - Source documents (lab reports, x-rays, etc.)
    - Signed consent forms and standalone HIPPA.
    - CRFs

Potential Endpoint or Serious Adverse Event

- Ensure that all required CRFs are completed and entered in WebDCU™ within 24 hours, excluding holidays/weekends, of first knowledge of the event.
- Upload relevant imaging to Ambra within 1 week.
- Upload de-identified event packet for any safety endpoint events on Adverse Event CRF

Communication with CCC and NDMC

- Establish and maintain an open line of communication with the project manager and other relevant personnel at the CCC, NCC, and NDMC
- Participate in all conference calls with the CCC, NCC, and NDMC

5.9.3 Primary Pharmacist

The primary pharmacist (PPh) at each site is responsible for overall study drug accountability for that site. This will typically be a licensed pharmacist who is experienced in clinical trials and qualified to participate in the receipt, storage, distribution, and record-keeping related to the investigational product (IP) in WebDCU™ study drug accountability module. Maintains records to meet sponsor requirements, FDA regulations and legal requirements for pharmacy operations.

The PPh is responsible for training and assisting other pharmacists/ CPS pharmacy staff regarding drug mixing, storage, accountability, and dispensing questions. They oversee the work performed by pharmacy technicians and identified staff to ensure that performance standards are maintained, and that work is accurate and in accordance with state, federal and organizational regulations.

6.0 Site Study Start-Up

Each site is required to complete a variety of contracts, forms, trainings, and activities prior to being released to recruit subjects. Please refer to section 7.0 Required Training and Training Plan for detailed information and instructions for trainings specific to the SISTER Trial.

6. 1 Contracts:

- **Confidential Disclosure Agreement (CDA):** a CDA must be fully executed between each site and Translation Sciences, Inc. prior to the release of the full protocol, investigator brochure, manuals of procedures, and clinical trial agreements.
- **Clinical Trial Agreement (CTA):** A standard CTA is used for all NIH StrokeNet trials. The agreement is not negotiable as all sites' agreements must be the same for trial

administrative purposes. The budget was approved by NINDS at the proposal funding stage. StrokeNet is utilizing the Federal Demonstration Partnership Fixed Rate Clinical Research Subaward Sample – NIH found at (http://thefdp.org/default/assets/File/Documents/subaward_forms/FDP_Clinical_Research_Sample_2019.pdf).

6.2 Central IRB (cIRB) Essential Documents/Forms:

cIRB Form	Information	Site Action Needed
Protocol Signature Page_v3.0	Current protocol signature page.	Site PI must sign. Upload to WebDCU™
SISTER Main ICF Template_v4_18Jul2023	We are using The University of Cincinnati central IRB (cIRB). No changes can be made to the consent template except as noted in the document.	Enter your site-specific information (blue font text). Email tracked and clean versions of consent form to Kim Lever at leverky@ucmail.uc.edu.
CIRB fCOI Form	Financial conflict of interest form.	Have each study team member sign and date with wet ink signature or CIRB approved form of eSignature. Email PI form to Kim Lever. All other team member forms to be filed at site. If a team member has a positive disclosure then that form must be returned with the PIs form
StrokeNet CIRB Assurance Statement	Permits cIRB to make the submission on the site's behalf. (Where the form says Principal Investigator, they are referring to the local site PI.)	Site PI must sign. Email to Kim Lever
StrokeNet Performance Site Application Supplement	Form collects information about your site for the cIRB application.	Complete form. Email to Kim Lever
Local Site Context Form	Form notifies your local IRB that you are preparing to submit to the cIRB at the University of Cincinnati for the SISTER trial. Requests for translated short forms should be included in each sites initial submission by completing section 1.c.3.	Complete form and email to Kim Lever for pre-review. After pre-review, send to official in your local IRB or HRPP office for signature. Email to Kim Lever after signature is obtained.
Partial HIPAA Waiver Request for screening purposes	Required for eligibility screening at your site.	Complete form and email to Kim Lever

Remote and Electronic Informed Consent Implementation Form	Form notifies cIRB if you plan to use remote and electronic informed consent at your site. If your site chooses to use eConsent please review attached GCP SOP 13 and StrokeNet Central eConsent SOP.	Complete form and email to Kim Lever
FDA Form 1572	FDA requirement	Please complete the editable sections and upload to WebDCU™. Instructions for completing this document can be found in the SISTER Regulatory Parameters Document in the WebDCU™ toolbox.

6.3 Site Specific Essential Documents:

Each site will have their own page in WebDCU™. All documents must be uploaded, reviewed, and approved prior to a site being released to enroll. This will be used to store all current site documents including but not limited to:

- Site cIRB approval letters
- ICDs both English and translated
- Translated short form ICDs
- HIPAA documents including site specific, if applicable
- Pharmacy License
- Local Lab Accreditation & Site Laboratory Standard Results
- Financial Disclosure Form(s)
- cIRB Approved Documents
- Local Drug Destruction Policy
- Site specific Bill of Rights
- Team Member personal documents needed for the study.

6.4 Summary of Required Trainings/Activities:

Complete details and instructions for all the required training section 7.0. Training assignments are based on tasks and roles assigned on the DoA.

Training/ Activity:	**Personnel Required to Complete:**	**Training/Information Location:**
WebDCU™ Navigation and Data Training	PSC, SSC, RDC, PI	https://webdcu.musc.edu/campus/
Human Subjects Protection Training	PSC, SSC, PI, Sub-I	Completed through CPS
Informed Consent Training	PSC, SSC, PI, Sub-I	Completed through CPS
eConsent Training	PSC, SSC, PI, Sub-I	https://redcap.research.cchmc.org/surveys/?s=YPDNMKFY4P
SISTER Protocol Training & Assessment	PSC, SSC, PI, Sub-I	https://webdcu.musc.edu/campus/
Coordinator Training & Assessment	PSC, SSC	https://webdcu.musc.edu/campus/

Pharmacy Training & Assessment	PSC, PPh, Ph, PI, Sub-I	https://webdcu.musc.edu/campus/
ASPECTS Training & Assessment	PI, Sub-I	https://www.letsgetproof.com/pages/aspect-in-stroke/homepage
RAPID AI	PSC, SSC, PI, Sub-I	Contact RAPID-AI
Individual Site Imaging Training	PSC, PI,	Contact IMC
Modified Rankin Scale	PSC, SSC, PI, Sub-I	https://webdcu.musc.edu/campus/
NIH Stroke Scale	PSC, SSC, PI, Sub-I	https://webdcu.musc.edu/campus/
Dry Ice Shipping	PSC, SSC, LP	Completed through CPS

6.5 Study Drug and Lab Shipments Received

- StrokeNet Central Pharmacy will ship the study drugs and materials that are being supplied.
- Each site must confirm receipt of shipment.

6.6 Site Readiness Call

Once a site has executed all contracts, received cIRB approval, has all essential site and personnel documents uploaded and approved, all study personnel have completed require training(s) and assessments SISTER Project Managers will reach out to schedule a site readiness call. The purpose of these calls is to refresh study teams on the initial training and address any questions. Once the call has been completed the study drug will be shipped.

7.0 Required Training and Training Plan

The goal of training is to ensure human subject protection and a full understanding of the protocol, as well as to standardize methods of data collection to allow for comparability of the data across all sites.

Training is an ongoing process. A monthly investigator/coordinator webinar will be held to review study progress and procedures, particularly those that may be problematic. These meetings will provide an opportunity for the investigators and coordinators to discuss mutual concerns and find solutions. The sessions will be valuable in providing an opportunity for communication, collaboration, and partnership. Similarly, a monthly coordinator webinar will be held to address updates, issues, and questions specifically to a study coordinator perspective.

Additional training will occur throughout the trial focusing on protocol compliance and site challenges. The training will be conducted by videoconferences, newsletters, email, and calls with site staff.

7.1 WebDCU Navigation and Data Training

To set up initial personal WebDCU™ login credentials during study startup, contact the SISTER WebDCU™ Data Managers.

After the study is started, anyone on the DOA who has ‘Maintaining Essential Regulatory Documents’ or ‘Regulatory Document Coordinator’ assignments can request WebDCU access for

new study team members under the 'User Management' tab.

All SISTER study personnel will be provided with a username and temporary password for the purpose of accessing WebDCU™. Study personnel will be prompted to change their temporary password the first time they log on to WebDCU™.

The link to the WebDCU™ database is: https://webdcu.musc.edu/login.asp.

WebDCU™ will be the Clinical Trial Management System (CTMS) that will house all study specific documents, data entry and regulatory maintenance.

Project Documents can be accessed by going to https://webdcu.musc.edu/login.asp, "SISTER → Toolbox → Project Documents" and includes but is not limited to:

- StrokeNet WebDCU™ User Manual
  - Contains step-by-step instructions for logging in to WebDCU™ and navigating the system for study specific tasks.
- SISTER Regulatory Document Parameter Guidelines for WebDCU™
  - Contains instructions specific for posting study required documents.
- SISTER Data Collection Guidelines
  - Contains general and specific guidelines for completion of CRFs.
- SISTER Randomization Instructions
- SISTER Manual of Procedures (MOP)
- SISTER Enrollment Tools
- SISTER CPS Study Drug Procedures
- SISTER Participant Correspondence Letters
- PRIME cIRB Approval Letters

SISTER-specific training modules are located at (https://webdcu.musc.edu/campus/ - Project Specific Training → SISTER Project).

7.2 Human Subjects Protection Training: It is the expectation that all investigators and staff involved in the conduct, oversight, or management of this NIH funded trial will be trained in Good Clinical Practice (GCP), consistent with the International Conference on Harmonization (ICH) E6. The principles of GCP provide study personnel a standard for ensuring trial compliance, implementation, data collection, monitoring, and reporting, for example, safety data, accrual reports, study status, protocol deviations, unanticipated events. All study staff members are required to have undergone Human Subjects Protection Training prior to participating in the SISTER trial. Documentation of such training will be uploaded to WebDCU™ and verified initially by the NCC Project Manager prior to site approval.

7.2 Informed Consent Training: All study personnel designated on the Delegation of Authority (DOA) log with the responsibility of obtaining informed consent on behalf of the trial must maintain current documentation of Human Subjects Protection Training in the WebDCU™ database.

7.3 eConsent training (if needed): The link to the required training will be included in the email that is sent to the site that contains the site's eConsent.

7.4 SISTER Protocol Training and Assessment

Principal Investigators, Sub-Investigators, Study Coordinators, and any other study personnel will undergo protocol-specific training and short assessment focused on:

- Study Objectives
- Inclusion and Exclusion Criteria
- Eligibility requirements
- Participant Visit Schedule
- Screening, Follow-up, and End of Study Visits
- Laboratory Evaluations
- Safety Monitoring and Reporting

The assessment is a short 5 question quiz located on MS Forms. After completing the quiz, click the “view results” button, then either print the page as a PDF or convert the page to a PDF. The PDF of results should then be uploaded into WebDCU™. The link to the assessment is listed on WebDCU™ Training page. A minimum of 80 points is required to pass. The results will be verified by the PMs.

7.5 Coordinator Training

Primary and secondary (if applicable) study coordinators will undergo a coordinator specific training focused on:

- Site start-up process
- Screening criteria
- Informed consent process
- Study medication procedures
- Study Labs
- WebDCU™
- Participant visit schedule
- Toolbox Resources

The assessment is a short 5 question quiz located on MS Forms. After completing the quiz, click the “view results” button, then either print the page as a PDF or convert the page to a PDF. The PDF of results should then be uploaded into WebDCU™. The link to the assessment is listed on WebDCU™ Training page. A minimum of 80 points is required to pass. The results will be verified by the PMs.

7.6 Pharmacy Training and Assessment

The pharmacy training and assessment will be focused on:

- General study drug information
- IP Storage
- Temperature monitoring and excursions
- Ordering, dispensing, preparation, compounding, and administration of the IP
- IP accountability, expiration/damage, and destruction/return

The assessment is a short 5 question quiz located on MS Forms. After completing the quiz, click the “view results” button, then either print the page as a PDF or convert the page to a PDF. The PDF of results should then be uploaded into WebDCU™. The link to the assessment is listed on WebDCU™ Training page. A minimum of 80 points is required to pass. The results will be verified by the PMs.

7.7 Laboratory Training

The laboratory training will be focused on:

- Specimen collection schedule
- Central lab kit, kit content, kit inventory, supply and resupply ordering
- Blood collection and plasma sample processing
- Plasma sample collection, storage, and records
- Sample Identification Form
- Specimen shipping/receiving and shipping schedule
- WebDCU™ procedures
- Discrepancies of items

7.8 Imagining Training

There are several trainings related to imaging that various study team members will need to complete.

7.8.1 ASPECTS

The ASPECTS in Stroke Education training is located at https://www.letsgetproof.com/pages/aspect-in-stroke/homepage. Thoroughly review the information listed on the webpage by scrolling through the images and clicking the “read more” buttons.

The ASPECTS in Stroke required quiz is located at https://www.letsgetproof.com/pages/aspect-in-stroke/homepage. The user will need to create an account log-in and then complete the quiz. A passing grade is 70%. Once a user has passed and obtained the ASPECTS in Stroke Certification, the certificate should be printed to a PDF and uploaded into WebDCU™.

The ASPECTS training certificate does not expire however, sites may need to be required to retrain if necessary.

7.8.2 RAPID

The initial RAPID software training will consist of the following:

- Self-paced, role-based, online end-user training via RapidU for the Institution; and
- Optional clinician-led live training via web conference to study personnel for use of the Rapid Software to aid in eligibility assessment as needed.

7.8.3 Individual Site Imaging Training

The central imaging center will reach out to each site to schedule and complete Ambra training.

7.9 Modified Rankin Scale Training and Certification Test:

Guidelines for performing the mRS assessment can be found in WebDCU™ (Toolbox/Project Documents/Data Collection Guidelines) and a resource link for mRS training certification can be found at (https://webdcu.musc.edu/campus/). Recertification will be required as per the stated expiration date on the certificate. If no expiration date is specified, recertification will be required 2 years from the date of completion as noted on the certificate. All certifications must remain current throughout the course of the trial.

7.10 NIH Stroke Scale Training and Certification Test: Guidelines for performing the NIHSS can be found in WebDCU™ (Toolbox/Project Documents) and a resource link for NIHSS training certification can be found at (https://webdcu.musc.edu/campus/). Protocol required NIH Stroke Scale (NIHSS) assessments should be completed by a study team member who has a

current NIHSS certification and is assigned that responsibility on the Delegation of Authority Log. Recertification will be required every 2 years from the date of completion as noted on the certificate. All certifications must remain current throughout the course of the trial.

7.11 Lab Specimen Shipping with Dry Ice: Training for shipping with dry ice should be completed through the resources provide at each CPS.

8.0 Communication Plan

Ongoing communication between the CCC, NCC, and CPSs is essential to ensure study progress and address emerging study issues. Communications will be maintained through, but not limited to, the mechanism listed below.

8.1 Site Directory

The SISTER site directory will be maintained by the PMs. Each site is responsible for updating study team members on the DOA in WebDCU™. The site directory will be available on the StrokeNet website https://www.nihstrokenet.org/ . It will also be listed in WebDCU™.

8.2 Hotlines and Email Address

8.2.1 SISTER Hotline: 1-866-212-7187

The SISTER Hotline is a toll-free number to be used for urgent and time sensitive enrollment and safety questions. The trial PIs will provide 24/7 coverage of this number to provide real-time answers to study related questions or concerns. All in-going, out-going calls, and SMS messages will be recorded.

8.2.2 WebDCU™ Emergency Randomization Hotline: 1-866-450-2016

The WebDCU™ Emergency Randomization Hotline is a toll-free number that is available 24/7 to investigators experiencing problems with performing randomization. This hotline should only be used for randomization emergencies.

8.2.3 SISTER Email Address: sister-trial@ucmail.uc.edu

This email inbox is for ***non-urgent*** study questions. The inbox is monitored by the Protocol and Contact PIs and project managers. All members listed are automatically notified of communications.

8.3 Newsletter

Trial newsletter will be sent monthly via email. These newsletters will contain enrollment updates, common problems and potential solutions, important reminders, upcoming events, and information on webinars and training.

8.4 Webinars

Two webinars will occur monthly by teleconference (1) Investigator/Coordinator webinar and (2) Coordinator-Specific webinar. The SISTER PIs along with Project Managers and NDMC will organize and facilitate these webinars jointly, although typically only Project Managers will attend the coordinator-specific webinar. Video and slides from the webinars will be posted on the SISTER section of the StrokeNet website: https://www.nihstrokenet.org/ .

All site team members are welcome to join monthly webinars.

8.5 Investigator Meetings

There will be a two start-up Investigator Meetings that will include a PI, coordinator, and primary pharmacist from each site:

1. Part 1: Overview of protocol, study activities, required trainings, and steps for release to enroll (January 2024)
2. Part 2: Overview of site startup status, detailed logistics for study screening and enrollment, refresher on protocol including study activities, and review of final steps for release-to-enroll (March 2024)

Site PIs, the primary site coordinator, and the primary pharmacist from each site must attend (or review online if not feasible to attend live). Other team members, including enrolling investigators and additional coordinators, are strongly advised recommended to attend these meetings. These meetings will serve as the initiation and protocol training for all site team members who are able to attend.

8.6 Executive Committee Meetings
The EC will meet twice annually for the full duration of the study (virtually or in person) to discuss the overall conduct of the study with regard to protocol compliance, modifications and amendments; study progress; and problem-solving.

8.7 Scientific Advisory Board (SAB) Meetings
The SAB will meet annually. The SISTER PIs will present study progress, updates, and challenges for review, feedback, and discussion.

8.8 Operations Meetings
The SISTER Operations committee will meet weekly to oversee the study and review its progress including ongoing safety and compliance issues.

8.9 DSMB Meetings
The DSMB will meet semi-annually and as needed depending on enrollment and findings as the study progresses. The organization for this meeting will be in coordination with NIH/ and NINDS staff. Minutes or response letters from this meeting will be submitted to the CIRB. Response letters will be shared with study sites.

9.0 Recruitment and Retention Strategy
SISTER trial aims to enroll 300 participants over 36 months at up to 50 active sites (average accrual rate of 2.6 patient per site per year). All active sites participating in the trial will screen and enroll consecutive patients who meet the trial criteria. *Particular diligence in screening will be required given how infrequently patients will be eligible.*

The study personnel will screen consecutive patients that meet the study eligibility criteria. The study personnel will not discriminate based on age, gender, race/ethnicity. Participants will be screened and enrolled in the emergency room of all CPSs. The study personnel will work with local treatment teams to identify potential participants.

The primary outcomes will be collected at 30±4 hours (i.e., during hospitalization). To enhance participant retention for key secondary and exploratory safety and efficacy outcomes, participants will be contacted (using telephone calls and/or mailed reminder cards) for the two subsequent visits at 30 and 90 days from enrollment, approximately 10 days before the respective visit. In addition to contact information for the participant, contact information for two additional next-of-kin or other contacts will be requested and recorded prior to discharge from the initial hospital stay. The 30-day visit will also serve as a reminder of the final study visit. At the 30 and 90-day study visits, patients will be compensated with $75 for their time and travel, assumed to be an

approximate one-hour time commitment, using the method of payment as approved by local site policies.

The Executive Committee of SISTER will monitor overall and site-specific retention. Site investigators will be encouraged to share best practices and lessons learned routinely during monthly webinars and investigator meetings.

9.1 Screening for Potential Participants

Below are some screening strategies that are considered best practices and are strongly encouraged:

1. Screening acute stroke pages.
2. Involve trainees (fellows, residents) and mid-levels who are involved in stroke calls.
3. Screening automated perfusion software output done as routine care.
4. Send weekly reminders to clinical staff.

9.2 Screen Failures

SISTER will collect screen failure data on patients with suspected acute ischemic stroke who present within 4-23 hours of last known well and are not treated with standard of care acute stroke reperfusion therapies, including thrombolysis and thrombectomy.

To ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities, the following will be collected demography, screen failure details, and eligibility criteria.

Below are common screening outcomes and how to the label them. If additional situations arise and further clarification is needed, please contact the SISTER team at sister-trial@ucmail.uc.edu . If none of the options listed apply, then please select “other” and provide a detailed explanation.

- Patients who are not consented are considered “screened, not consented” (screen failures). These should be entered in the screening log.
- Patients who are consented but are not randomized due to study imaging ineligibility or other reasons, are considered “consented, not randomized.” These should be entered in the screening log.
- A participant, who is both randomized and received study drug initiation, is in the modified Intent-to-Treat (mITT) population.
- Patient who is enrolled in another clinical treatment trial should not be considered and listed as “screened, not consented” (screen failures).
- A patient that refuses participation should be listed “screened, not consented” (screen failures).

9.3 Monitoring Recruitment

The NDMC, in conjunction with the operations team, will monitor recruitment. Screen failure logs will be reviewed monthly to identify recruitment problems. Protocol PI will work directly with sites to troubleshoot recruitment problems. This monitoring activity will enable the team to identify any problems with recruitment and to redirect recruitment resources, if necessary. A Cumulative Recruitment Summary Report retrievable from WebDCU™ will detail the numbers of patients screened, enrolled, and randomized.

1. Sites will generally need to have a non-enrollment call with the SISTER National Team if they have not consented any patients for 6 consecutive months.

2. Sites may be placed on probation if after an additional 6-month period no patients have been consented.
3. Sites may be suspended if after an additional 4-month probation period they still do not have any consented patients.
4. Sites may also be put on probation if they have 3 consecutive patients who meet randomization criteria based on screening but are not randomized.

9.4 Participant Retention

Every effort will be made by the site PI and study team to ensure participants complete each study visit and evaluation for the trial. The following strategies should be used to help maximize retention and minimize participant lost to follow-up:

- Building participant relations and subject satisfaction, with the study coordinator taking a central role on this effort
- Giving participants and their families the opportunity to ask questions and express concerns.
- Informing subjects of the anticipated length of the 30- and 90-day follow-up visits
- Enhancing participant's and their families understanding of the participant's objectives and the protocol by reminding the participant of the study aims during reminders for the follow-up visits.
- Maintain contact by phone or email between discharge and the 30- and 90-day follow-up visits.
- Schedule 30-day and 90-day follow-up visits prior to hospital discharge and provide the participant with a study visit reminder card.
- Provide reminders via email and/or phone-calls approximately 10-days prior to the schedule visit.
- Collect patient contact information including phone number(s), email address, and contact information for two next-of-kin or other contacts.

9.5 Lost to Follow Up

The primary outcomes for SISTER are collected at 30 (±4) hours after drug administration. Almost all participants will be in hospital at the time of the 30 (±4)-hour follow up visit. All effort should be put forth to ensure complete follow-ups for all randomized participants. Only in *very* rare instances should this assessment not occur as the majority of patients will be admitted to the hospital at least for the duration of 24-30 hours following their acute stroke.

To ensure successful completion of this visit within the window, the following steps should be taken:

- Study personnel will note the patient's name, date-of birth, and medical record numbers upon enrollment.
- Clearly communicate and remind the clinical care teams about the study assessment timeline from time-to-time.
- The imaging and NIH Stroke Scale score assessment by certified rater should be scheduled immediately after study drug administration.
- The follow up imaging should be a part of the hospital electronic medical record study order-set.
- The timing of the scan and assessment should be communicated and coordinated with bedside nursing staff and imaging technologist.

The 30 and 90-day follow-up visits should be scheduled prior to the participant being discharged. If it is not, then multiple attempts should be made to reach the participant. If the participant cannot be reached, multiple attempts should be made to the person(s) listed as secondary contact. If no contact is made after multiple attempts, alternative methods should be considered to obtain contact with the participant and/or verify their living status. Examples of alternative methods of contact are fax, other scheduled medical appointments, and certified letter.

Efforts should be made for up to 150 days from randomization to retrospectively determine the participants' 90-day status. A participant may be considered lost to follow-up if they cannot be reached for up to 150 days from randomization, despite following the procedures outlined above. Appropriate documentation of lost to follow-up will be maintained in the participant's research record at the site.

The following are reasons a participant is considered lost to follow-up:

- Unable to contact for follow-up.
- Opted to withdraw from the trial.
- Moved away from and unable to return for follow-up visits.
- Became ill and unable to communicate.

Subjects who sign the informed ICD and are randomized but do not receive the study drug may be replaced. Subjects who sign the ICD, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn from the study, will not be replaced.

9.6 Withdrawal of Consent

A participant or their legally authorized representative may decide at any time during the study to no longer participate in the study. Every study participant has the right to withdraw voluntarily from the study at any time for any reason without prejudice to his or her future medical care by the physician or at the institution. Participants wishing to revoke their authorization for the research use or disclosure of health information must do so in writing to the site PI as outlined in the informed consent form provided to the participant at the time of consent. Written correspondence revoking consent should be retained in the study participant's file in a secure and confidential manner. Participant data collected prior to the time of withdrawal will remain as part of the study records. The reason for participant withdrawal from the study should be recorded on the CRF.

If the participant withdraws the study team should ask the participant if they are willing to allow further medical information to be collect from their routine medical care.

Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

10.0 Eligibility Criteria

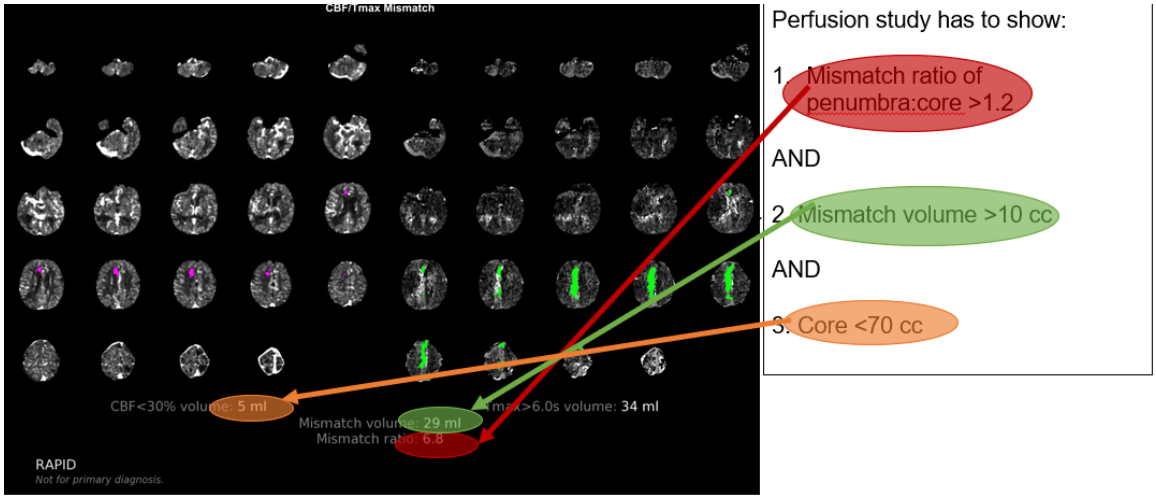
Always refer to the current approved protocol for the most up-to-date inclusion and exclusion criteria. *Further explanations of eligibility criteria are detailed in italics below*.

10.1 Inclusion Criteria

1. Age 18 years and older

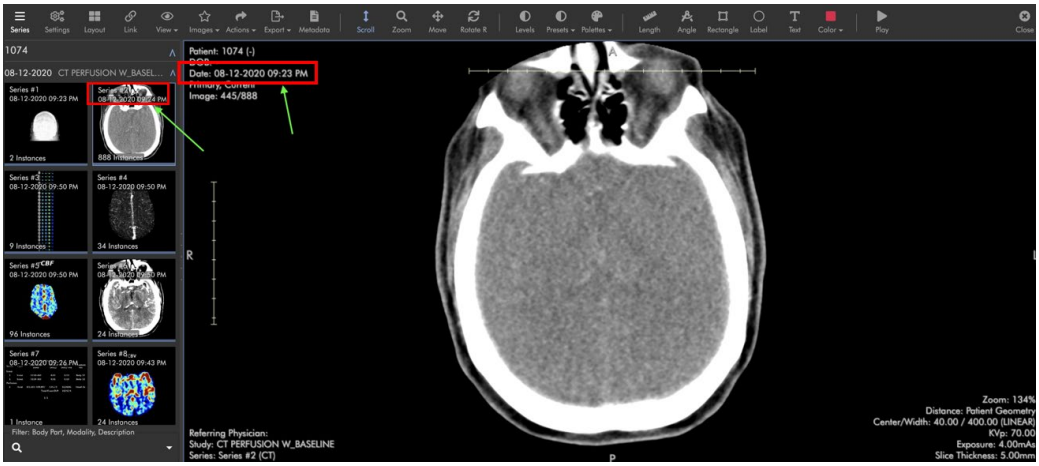
2. Suspected anterior circulation acute ischemic stroke.
3. Presenting NIH Stroke Scale score ≥ 6
    a. *This is the most recent NIHSS score prior to randomization. If consented and then NIHSS decreases below 6, then patient should not be randomized and should be logged as a screen failure.*
    b. *If a patient is transferred from another facility with an NIHSS score, the score assessment should be readministered at the treating hospital. The most recent NIHSS score prior to randomization should be used for enrollment.*
4. Favorable baseline neuroimaging consisting of all of the following:
    a. ASPECTS of 6 or more on CT (or ASPECTS of ≥ 7 on MRI)
        i. *ASPECTS should be calculated based on loss of grey-white differentiation not edema.*
    b. Favorable perfusion imaging on CT perfusion (CTP)/MR-perfusion weighted imaging (PWI) consisting of all of the following:
        i. Mismatch ratio of penumbra: core >1.2
        ii. Mismatch volume >10 cc
        iii. Core <70 cc

    This is the EXTEND trial criteria which are more inclusive than the DEFUSE-3 criteria. This should be evaluated on the local automated perfusion processing software (Viz, RAPID, aidoc, etc.)



    c. Please see section 13.1 Qualifying Imaging Section for details
5. Able to receive assigned study drug within 4.5 to 24 hours of stroke onset or last known well.
6. Able to receive assigned study drug within 90 minutes of the acquisition of the qualifying perfusion imaging.
    a. *Study drug administration is encouraged within 60 minutes after qualifying perfusion image but is allowed up to 90 minutes. After 90 minutes, another perfusion image to ensure that inclusion criteria are met is required.*

b. *Acquisition time can be found on the perfusion source image as a time stamp.*



7. Informed consent for study participation obtained from participant or their legally authorized representative.

    a. *Electronic consent (or paper scanned into REDCAP if necessary) is the preferred approach. Remote consent via electronic consent is permissible.*

10.2 Exclusion Criteria

1. Plan to receive endovascular treatment.

    a. *May reassess if plans change and endovascular therapy is no longer planned or could not be initiated*.

2. Received or plan to receive IV thrombolysis.

    a. May reassess if plans change.

3. Pre-stroke modified Rankin score >2.

    a. Rankin focused assessment is not required for this score. As a reminder, mRS>2 means unable to take care of oneself independently.

4. Previous treatment with TS23 or known previous allergy to antibody therapy.
5. Known pregnancy, women who are breastfeeding or plan to breastfeed within 3 months of receiving TS23 or have a positive urine or serum pregnancy test for women of childbearing potential.
6. Known previous stroke in the past 90 days.
7. Known previous intracranial hemorrhage, intracranial neoplasm, subarachnoid hemorrhage, or arterial venous malformation.

    a. Meningioma is not an exclusion. Meningioma patients are allowed in the study unless it is known to be malignant or anaplastic.

8. Known active diagnosis of intracranial neoplasm.
9. Clinical presentation suggestive of a subarachnoid hemorrhage, even if initial CT scan was normal.
10. Surgery or biopsy of parenchymal organ in the past 30 days.

11. Known trauma with internal injuries or persistent ulcerative wounds in the past 30 days.
12. Severe head trauma in the past 90 days.
13. Persistent systolic blood pressure >180mmHg or diastolic blood pressure >105mmHg despite best medical management.
    a. *Elevated blood pressure despite treatments such as IV nicardipine.*
14. Serious systemic hemorrhage in the past 30 days.
15. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with International Normalized Ratio (INR) >1.7.
    a. *Confirm normal range value before randomizing.*
16. Platelets <100,000/mm3.
    a. *Confirm normal range value before randomizing.*
17. Hematocrit <25 %.
    a. *Confirm normal range value before randomizing.*
18. Elevated aPTT above laboratory upper limit of normal.
    a. *Confirm normal range value before randomizing.*
19. Creatinine > 4 mg/dl, or patients receiving renal dialysis, regardless of creatinine.
    a. *Confirm normal range value before randomizing.*
20. Received heparin or low molecular weight heparins (such as Dalteparin, Enoxaparin, Tinzaparin) in full therapeutic dose within the previous 24 hours.
21. Received Factor Xa inhibitors (such as Fondaparinaux, apixaban or rivaroxaban) within the past 48 hours.
22. Received direct thrombin inhibitors (e.g., argatroban, dabigatran, bivalirudin, desirudin, lepirudin) within 48 hours.
23. Received glycoprotein IIb/IIIa inhibitors within the past 14 days.
24. Known pre-existing neurological or psychiatric disease, which would confound the neurological/functional evaluations.
25. Current participation in another research drug treatment protocol (i.e., participants could not start another experimental agent until after 90 days).
    a. *Co-enrollment in an observational study is permitted.*
26. Concurrent acute myocardial infarction, pulmonary embolism, deep venous thrombosis, or other thrombotic event that requires anticoagulation or anti-platelet treatment.

11.0 Informed Consent

In accordance with FDA regulations (21 CFR 50) and International Council for Harmonization-GCP Consolidated Guidelines, CIRB-approved, informed consent is required from all patients prior to study participation. All qualified SISTER study personnel designated on the DOA log with

the responsibility of obtaining informed consent on behalf of the trial must provide documentation of acceptable HSP Training.

The CPS PI is responsible for ensuring that a signed and dated informed consent document (ICD) is obtained from each participant or legally authorized representative (LAR) before the patient participates in any study related activity even when this task has been delegated to other individuals on the study team.

This study will be utilizing REDCap eConsents. The SISTER trial highly encourages the use of eConsent as the primary modality of consenting participants. REDCap is a mature, secure web application for building and managing online surveys and databases. It facilitates presentation of an electronic Informed Consent Document (eICD) and capturing the patient's signature. To access and complete the eICD, the patient must have access to a smartphone, tablet or computer with Wi-Fi or cellular internet connectivity. Individuals provide a handwritten signature by using a computer mouse, or by using their finger on a cell phone or tablet touchscreen. (Printing out the ICD, signing, and then uploading it remains a secondary option if necessary.) REDCap automatically saves the signed eICD on its secure server and maintains an audit trail that logs all user actions.

11.1 Informed Consent Best Practices

The ICF should be the basis for a meaningful exchange about the study between the investigator or other designated member of the study staff as documented on the DOA and the patient and/or LAR. The guidelines for basic elements of the informed consent process and documentation required are specified in the StrokeNet SOP Number: GCP 03.

Please keep the following in mind before you begin the consenting process:

1. Confirm the use of the most current cIRB approved ICD prior to initiating the consenting process.
    a. The most current paper ICD can be found in the in the WebDCU™ space holder, under regulatory documents.
    b. Electronic consent forms in RedCAP are updated to the most current version by the NCC project manager.
2. Informed consent must be obtained prior to ANY study related activities.
    a. If a perfusion imaging study is not standard of care (SOC) at your site, then that patient will need to be consented prior to completing the perfusion scan to determine if they meet the imaging inclusion criteria.
3. The ICD and all associated documents must be in the language the patient or LAR is fluent.
    a. Requests for translated ICD and/or short forms should be submitted with initial cIRB approval.
    b. If a CPS uses a standalone HIPPA form and/or patient Bill of Rights and the site has a translated ICD, then the CPS is responsible for translating those documents.
        i. It is recommended that the HIPPA form and Bill of Rights be included in the ICD. If they are incorporated into the ICD, then the NCC will provide the translation.
        ii. Please see section 11.3 Foreign language ICD for details.
4. The ICD should be signed AND dated by the patient or LAR to permit verification that consent was obtained before the participant began participation in the study.

5. The time and date of informed consent should be documented in the participant's medical record with a note that consent was obtained prior to the participation in the study.
6. Informed consent can be obtained from an LAR if patient is deemed decisionally impaired.
    a. Who qualifies as LAR depends on state law and generally such representatives include parents and legal guardians, spouses, adult children, adult siblings or a person that is legally authorized to make such a decision.
    b. If no LAR is available and the individual is unable to give consent, the prospective participant can NOT participate in the SISTER trial.
7. The original ICD should be retained in the study/participant file in a secure/confidential manner. E-consent is strongly encouraged to minimize errors, even if consenting person is in person. Whether consent is completed on paper or electronically, it should be stored electronically with appropriate access, with all signed consent version easily retrievable.
8. A copy of the ICD must be provided to the participant.
    - FDA regulations do not require the participant's copy to be a signed copy, although with signature(s) is preferred and can be forwarded by email (or printed) as part of the eConsent process.
9. A non-redacted ICD will be uploaded by local site coordinator into WebDCU for remote monitoring by NDMC personnel.
10. CPSs must adhere to any additional local site requirements for the management and storage of ICDs. This NIH funded trial requires all study files to be retained over the life of the trial award and at a minimum of 5 years beyond the date of trial publication.

11.2 Foreign Language ICD

Translation and utilization of foreign language ICDs will be conducted according to StrokeNet SOP Number: ADM 26. The SOP can be found here: https://nihstrokenet.org/docs/default-source/default-document-library/26-adm-sop--final.pdf?sfvrsn=0

You may only request translation of the full ICD in Spanish as per our standard StrokeNet approach. To be prepared to consent in foreign languages other than Spanish, please obtain translated short forms for the most common languages in your region during the start-up cIRB process.
If a translated short form is used, you will have 30 days from the time of consent to obtain the fully translated documents and re-consent the participant using these forms. Please contact the NCC PM to obtain the fully translated ICDs, as necessary.

11.3 Informed Consent via Telemedicine or Telephone

In addition to eConsent, other methods such as telemedicine or telephone, may be used to obtain informed consent remotely following StrokeNet SOP GCP 13.

During the start-up phase, an Implementation form will need to be completed indicating your site's desire to use remote processes, eConsent process, or both. This form will be submitted with your start-up packet documents to the cIRB for approval. Remote consent may only be obtained using the processes for which your site is approved.

11.3.1 REDCap eConsent Process

Obtaining consent utilizing the centrally managed REDCap eConsent platform should be conducted according to StrokeNet SOP ADM 24.

Site-specific eConsent forms will be built within REDCap and a site-specific link will be provided by the NCC. This static URL can then be share with the patient/LAR. The person obtaining consent will review the eICD and provide instructions on completing the form. The patient or LAR

will add their handwritten signature. Upon completion of eICD, the site's study team will receive the completed eICD PDF via automated email. The participant or LAR may elect to receive the eICD PDF via email. When the study team and the patient or LAR are not in the same physical location, both parties are not able to sign the eICD at the same time. Only the patient or LAR will sign in real time and the person obtaining consent will subsequently complete a remote consent attestation form.

NCC personnel are responsible for creating a REDCap project for each site, ensuring that the most recent CIRB-approved version of the site-specific ICF is available in REDCap for eICD use, providing the site with their cIRB approval to use the central eConsent process, providing access to their study-specific and site-specific REDCap project, and maintaining the list of individuals who receive the completed eICD PDF via automated email according to the site's DOA in WebDCU.

CPS's responsibilities are to designate a primary and back-up user to access to their REDCap eConsent project, ensure the Remote Consent Attestation is completed, when required, by the person who obtained consent remotely, and ensure the PDF versions of the eICD and Remote Consent Attestation, as applicable, are combined into one document and uploaded to WebDCU within 5 days of signature.

11.4 Reconsenting a Participant

If there are significant changes in the SISTER protocol during the course of the trial, the cIRB may require that all active participants be reconsented. Ideally, reconsenting should be done in person and mirror the initial consenting process; however, situations may occur that makes this impractical. Therefore, reconsent may be obtained remotely using REDCap e-Consent, fax, or mail (postal service) in accordance with cIRB policies. Prior to reconsent, participants should be presented with a revised consent that includes the new study information and have all questions answered to their satisfaction. Participants should sign the revised consent to continue to participate in SISTER.

If reconsent is needed and you would like to use the remote process, your site must be approved to use this process by completing an Implementation form and obtaining approval from the cIRB. Please reach out to the NCC PM to initiate this process.

12.0 Randomization

12.1 Submitting the Randomization Form

Once it is determined that a patient meets all the eligibility criteria and signed and dated informed consent is obtained, individuals with the delegated responsibility to perform randomization will log on to the secure, study-dedicated clinical trial management system (WebDCU™) to complete brief Enrollment and Randomization Case Report Forms, including pertinent demographics and randomization data. Of note, consenting and randomization must take place during the initial visit. The site investigator or designee must confirm that eligibility criteria have been met prior to submitting the Randomization Form. The database will assign the participant a study ID number and immediately randomize the participant to a treatment arm.

12.2 Steps for Randomization in WebDCU™

These are the basic steps that will need to be completed to randomize a participant. Detailed SISTER specific instructions can be found in Appendix 1 “SISTER Randomization Instructions” or in the Project Documents in the SISTER WebDCU™ database.

1. Click on [Add New Subject] and complete the Subject Enrollment form with the demographic information. Once completed and saved, a Subject ID number will be generated. You will find a green arrow on this screen next to Subject CRF Binder. Once you click on this, you will be taken to the CRF Binder.
2. Click on [F102 Randomization], and enter the required data, including the baseline covariates and weight information for dosing.
3. Once F102 has been saved and submitted, a unique randomization code will be populated in C02. Click on the green arrow in C05 to obtain the Randomization Verification Form. This Randomization Verification Form will need to be taken to the unblinded site pharmacist, so they can mix and dispense the assigned study drug.

12.2 Enrolled vs. Randomized

A participant is NOT considered enrolled in the trial until study drug is initiated. Once study drug is initiated the participant should be followed until study completion. If a participant is randomized and study drug is not initiated for any reason the participant WILL NOT be followed and that participant will be replaced.

12.2 Hotlines for Time-Sensitive Communication

Two hotlines are available 24/7 for urgent communication:

1. **SISTER Clinical Hotline**: For questions regarding eligibility or protocol implementation, please contact: 1**-866-212-7187**

2. **WebDCU™ Emergency Randomization Hotline:** For questions or difficulties with randomization process, please contact **1-866-450-2016**.

13.0 Imaging

This section includes only some details regarding the required images for the SISTER Trial. Please refer to the Imaging MOP for full procedural details and instructions. Any additional questions should be directed to the NCC, Prime, and Imaging PMs.

13.1 Qualifying Imaging

If perfusion imaging was not performed as part of standard of care, it will be required as a study procedure to determine study eligibility of the patient after obtaining informed consent. Choice of imaging modality (i.e., CT vs MRI) for the perfusion study is based on what is routinely performed as standard of care at your institution.

Regardless of bassline qualifying imaging modality all participants will receive a *non-contrast CT scan* at the 30 (±4) hour visit. If a participant received an MRI at baseline, then they should have both a MR Perfusion and MRA scans AND a CT.

13.3 Imaging Submission to the Imaging Management Center (IMC)

- It is expected that all head and neck imaging performed within 72 hours from stroke onset or LKW (i.e., NCCT, CTA, CTP, MRI, MRA, MRP) will be submitted to the IMC.
    - Imaging to be submitted inclusive of baseline imaging to determine trial eligibility and follow-up imaging at 30 hours (+/- 4 hrs.) after study drug administration as well as other head imaging obtained for any clinical deterioration.
- It is the responsibility of the clinical site, in collaboration with the site's Radiology Department, to oversee protocol required image acquisition as well as the timely transmission of the images via the secure Ambra Health® platform to the IMC for subsequent central interpretation.

Ambra Health®

- Is accessed directly from your internet browser
- Requires no separate software download
- Is HIPAA compliant
- EU GDPR compliant for lawful processing of participant health data
- GCP and 21 CFR Part 11 compliant
- Image data is shared via secure web link only accessible by authorized personnel

Imaging ***MUST BE* submitted to the IMC within 5 to 7 days of participant randomization.**

- If the 5–7-day timeline cannot be met for any reason, it is the site's responsibility to communicate reason for delay to the IMC project manager. The IMC will work closely with the site to address any issues/challenges related to meeting this requirement.

Imaging data received at the IMC will undergo a thorough quality inspection to assess protocol adherence and technical quality (e.g., ensure de-identification of all protected health information [PHI], assess for missing images, corrupt imaging data, etc.). Data clarification requests (DCR) will be generated through WebDCU™ and/or email to resolve any imaging issues identified during this inspection. A persistent pattern of failure to meet pre-specified imaging criteria from a site will be cause for Sponsor notification by the IMC.

- After the imaging passes QA/QC, it will be made available on the secure Ambra Health® platform for the designated central reader to perform timely independent blinded review on submitted imaging studies.
- Imaging data will subsequently be shared via a OneDrive folder with NDMC statisticians.

Refer to the SISTER Imaging Manual document for detailed imaging data transfer instructions located in WebDCU™ under "ToolBox"→"Project Documents".

14.0 Laboratory Studies

All research related specimens must be drawn from a dedicated venipuncture. All SOC lab specimens should be drawn as dictated by local institutional policy.

Lab Specimen	Timepoint	SOC or Research
Pregnancy Test	Baseline	SOC
Glucose	Baseline	SOC
Creatinine	Baseline	SOC
HgbA1C	Baseline or at any point during hospitalization	SOC

Total Cholesterol	Baseline or at any point during hospitalization	SOC
HDL	Baseline or at any point during hospitalization	SOC
LDL	Baseline or at any point during hospitalization	SOC
Triglyceride	Baseline or at any point during hospitalization	SOC
aPTT	Baseline	SOC
PT	Baseline	SOC
INR	Baseline	SOC
CBC	Baseline	SOC
Platelet Count	Baseline	SOC
Fibrinogen	Pre-study drug administration	Research- processed & resulted locally
α2AP	Pre-study drug admin.	Research- sent & resulted at the central lab
MMP-9	Pre-study drug admin.	Research- sent & resulted at the central lab
PK	Pre-study drug admin.	Research- sent & resulted at the central lab
Fibrinogen	Post-study drug admin. 3 +/-1 hr.	Research -processed & resulted locally
α2AP	Post-study drug admin. 3 +/-1 hr.	Research- sent & resulted at the central lab
MMP-9	Post-study drug admin. 3 +/-1 hr.	Research- sent & resulted at the central lab
PK	Post-study drug admin. 3 +/-1 hr.	Research- sent & resulted at the central lab
Fibrinogen	Post-study drug admin. 30 +/-4 hrs.	Research- processed & resulted locally
PT/INR	Post-study drug admin. 30 +/-4 hrs.	Research- processed & resulted locally
aPTT	Post-study drug admin. 30 +/-4 hrs.	Research- processed & resulted locally
α2AP	Post-study drug admin. 30 +/-4 hrs.	Research- sent &resulted at the central lab
MMP-9	Post-study drug admin. 30 +/-4 hrs.	Research- sent & resulted at the central lab
PK	Post-study drug admin. 30 +/-4 hrs.	Research- sent & resulted at the central lab
CBC	Post-study drug admin. 30 +/-4 hrs.	SOC
α2AP	90-day follow-up visit	Research- sent & resulted at the central lab
MMP-9	90-day follow-up visit	Research- sent & resulted at the central lab
PK	90-day follow-up visit	Research- sent & resulted at the central lab
Anti-drug antibodies	90-day follow-up visit	Research- sent & resulted at the central lab
CBC	90-day follow-up visit	If collected as SOC
CMP	90-day follow-up visit	If collected as SOC
Lipid Profile	90-day follow-up visit	If collected as SOC

15.0 Study Drug, Dosing, and Administration

15.1 Study Drug

- TS23 a chimeric monoclonal antibody that inactivates a2-antiplasmin (a2AP). TS23 is manufactured under the direction of Translational Sciences, Inc. by Cytovance Biologics, Inc.
- TS23 will be provided in 10ml vials at a concentration of 10mg/ml (100mg/vial).
- Store TS23 in a secured, limited access area at 2-8°C (36-44°F) and protected from light. Storage of the investigational product (IP) must be compliant with the instructions provided by the Central Pharmacy (CP).
- IP should only be used in accordance with the protocol and for participants consented in the trial.

Note: Detailed site requirements, storage instructions, and pharmacy instructions for the trial are provided in the SISTER Site Pharmacy Manual.

15.2 Dose Assignments

Five different TS23 doses will be studied. Based on future analysis one of the dose arms/cohorts may be discontinued:

Cohort 1: placebo (for TS23)

Cohort 2: 3.0 mg/kg TS23

Cohort 3: 5.0 mg/kg TS23

Cohort 4: 7.0 mg/kg TS23

Cohort 5: 10.0 mg/kg TS23

The doses will be administered according to the doses listed in the table below. Always adhere to the dosing information populated on the Randomization Verification Form for each participant.

Dosing Based on Participant's Weight

TS23 dose mgs				
Weight (kg)	**3 mg/kg**	**5 mg/kg**	**7 mg/kg**	**10 mg/kg**
<60	180	300	420	600
60 to <70	210	350	490	700
70 to <80	240	400	560	800
80 to <90	270	450	630	900
≥90	300	500	700	1000

15.3 Study Drug Administration

- Study drug infusion needs to start within 24 hours of LKW **AND** within 90-minutes of the qualifying perfusion image acquisition time.
- All participants will receive a single, blinded dose of either 200 ml of study drug solution or 200 ml of 0.9% saline (placebo) given intravenously over 15 minutes.
- At the highest dose of TS23, this corresponds to a maximum rate of 0.67 mg/kg/min.
- The study drug or placebo solution should be administered through a dedicated line as a primary infusion through a pump.
- Some of the contents of the 200 ml study drug solution may be left in the IV tubing once the pump system turns off. The IV tubing must be flushed with at least 40 ml of 0.9% saline to ensure the full 200 ml of study drug is administered to the participant.

The study drug will be diluted by the study pharmacist with sterile 0.9% saline to a total volume of 200 ml for infusion as described in the Pharmacy Manual.TS23 diluted for infusion with 0.9% saline and 0.9% saline have a similar appearance. The diluted study drug or placebo will be given to the study team by an unblinded site pharmacist without indication of the identity of the drug, so as to maintain blinding.

The study drug will be administered by the clinical team which will be educated by the research team. It is the responsibility of the research team to document or confirm the clinical documentation of study drug start time, stop time and any interruptions.

15.3.1 Study Drug Administration Observation

The patient should be closely monitored following study drug administration for *at least* 4 hours following the study drug infusion for development of adverse reactions and without disruption of standard clinical care. Sites should follow their usual post thrombolysis care and admit the patient to the unit that can provide this type of care.

15.4 Discontinuation of Study Drug

- No dose reductions are allowed in this study. Temporary interruptions in the administration of study drug infusions, other than brief ones to address a blocked IV line, are also not allowed in this study.
- It is expected that all randomized participants will receive the complete treatment, unless there is a safety issue that prevents completion of the infusion. If the patient develops hemorrhagic complications or anaphylaxis to the drug administration, the study medication may be halted. In such an event, the patient will be treated for the complications per the site PI's best judgement.
- If there is a need to interrupt administration of the study drug infusion because of a safety concern, then study drug administration must be permanently discontinued. The reason for discontinuation and the amount of dose administered will be documented.
- Information regarding the type of reaction leading to discontinuation of study intervention, total duration of administration, total dose administered, and treatment needed for the reaction will be noted on the CRF. The event responsible for study drug discontinuation will be noted as an AE or SAE and/or UP.
- Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.
- If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the site PI or qualified designee will determine if any change in

participant management is needed. Any new clinically relevant finding will be reported as an SAE or AE.

15.5 Rescue Medicine

In case of symptomatic ICH or major systemic bleeding event, antifibrinolytic agents such as

epsilon amino caproic acid (Amicar) or tranexamic acid (Lysteda) should be considered and used according to the package insert.

15.6 Concomitant Stroke Care

Stroke care of the participant should be maintained throughout the participant's participation in the study according to the American Heart Association/American Stroke Association Get With The Guidelines®. In particular, the blood pressure should be maintained </=180/105 mmHg.

16.0 Unblinding

Unblinding can occur if there is an emergency clinical need to know the participant's treatment assignment. These clinical emergencies include but are not limited to:

- A severe allergic reaction
- Recurrent ischemic stroke during the index hospital stay
- A significant, continuing bleeding event, such as a major hemorrhage, that requires ongoing and urgent pharmacologic or surgical intervention
- The need for emergency major surgery (for example, open cardiac procedures, open neurosurgical procedure, etc.)

Unblinding may not be necessary for these emergencies if 15 days have passed since the administration of study intervention, because of the drug's half-life.

16.1 Unblinding Requests

For any emergency request for unblinding, the site investigator or emergency care provider should:

- Call the SISTER clinical hotline 1-866-212-7187
- Discuss the case with the SISTER PI on call, who will evaluate the clinical scenario promptly, including review of conditions whereby unblinding may not be necessary.

If the request to unblind is determined to be appropriate, the SISTER PI who received the request should follow the steps below to unblind the participant's treatment assignment.

16.2 Unblinding Directions for National PI

1. Login to WebDCU™ (https://webdcu.musc.edu/) and select the [Safety Monitoring] tab and then select [Treatment Unblinding].
2. Select the 'Add New' button located in the top right corner of the page.
3. Complete the Treatment Unblinding form:

   Subject: Select the subject to be unblinded from the drop-down list. To quickly find a subject ID, begin typing the number in the field.

Site: Once the Subject ID has been selected, you will be able to select the subject's enrolling site. While only one option will be available in this field, you will need to select the site from this drop- down field.

Requested by: Indicate if unblinding was requested by the subject's treating physician or by a study.
team member

Reason for unblinding: Enter the reason for unblinding.

Notes: This field is optional and can be used to document any other relevant information about the unblinding.

4. Once the Treatment Unblinding form is complete, select the 'Save Record' button at the bottom of
the screen.
5. After saving, select the 'List Record' button in the top right of the page.
6. On the list record page, the subject's treatment assignment will be shown under the 'Treatment' column. The treatment assignment will display as one of the following: 3 mg/kg, 5 mg/kg, 7 mg/kg, 10 mg/kg or Placebo.
7. Also, on the 'List Record' page, the subject's 'Gender' and 'Date of informed consent' will be shown. This information is intended to be used to verify that unblinding has been requested for the correct subject before providing unblinding information to the requestor.
8. Treatment assignment will be available in this view for 30 minutes. After 30 minutes, the subject unblinding record will remain, but the 'Treatment' field will be blank.

Subjects who are unblinded will not be resumed on study drug but will continue to be followed and analyzed per the intent-to-treat principle.

If unblinding occurs due to a major bleeding event for a patient who received active drug, the SISTER PI on the hotline call may discuss potential drugs for hemostasis with the site.

17.0 Study Visits and Assessments

Schedule of Activities								
			Time after initiation of study drug administration					
	Baseline	**Study drug administration**	**3 (±1) hours**	**30 (±4) hours****	**72 (±12)/ Discharge Visit (whichever is 1st)**	**Discharge Visit**	**Day 30±5**	**Day 90±7**
Screening & Eligibility	X^R							
Medical History	X^S							
Laboratory Studies	X^S & X^R	X^{R*}	X^R	X^S & X^{R**}				X^R
Pre-stroke mRS	X^R							
NIH stroke scale	X^R			X^R	X^R		X^R	X^R
Vital Signs	X^S			X^S				
CT brain	X^S			X^S or X^R				
CT/MR Perfusion	X^S or X^R			X^R				
CTA/MRA Head & Neck	X^S			$X^{R\#}$				
Informed Consent	X^R							
Randomization	X^R							
Study drug administration		X^R						
Discharge Summary						X^S		
Concomitant Medications	X^S	X^R	X^R	X^R	X^R	X^R	X^R	X^R
Adverse Events		X^R	X^R	X^R	X^R	X^R	X^R	X^R
Serious Adverse Events		X^R	X^R	X^R	X^R	X^R	X^R	X^R
mRS						X^R	X^R	X^R
End of Study								X^R

X^S: Standard of Care; X^R: Research Procedure; D/C = Discharge; CTA/MRA = CT pr MR Angiogram; mRS: Modified Rankin Scale score
*PK/PD & Fibrinogen lab draw BEFORE and 3(+/-1) hour after study drug administration
**PK/PD, Fibrinogen, PT/INR, PTT and CBC SOC lab draw 30(+/-4) hour after study drug administration
#Required only if visible vessel occlusion present on the baseline CTA or MRA per site read

17.1 Baseline

- Patients presenting with acute ischemic stroke should be evaluated in accordance with institutional practices to establish eligibility.

- Only the Subject Enrollment form needs to be completed in WebDCU™ prior to randomization.

- Participants enrolled ***should not*** receive antithrombotics for *at least* 24 hours after study drug administration.

    - The study order sets should specifically include an order to not administer antithrombotics within the first 24 hours after study drug administration.
    - This should be closely monitored and there should be no disruption to standard clinical care. Sites should follow their usual post thrombolysis care and admit the patient to the unit that can provide this type of care.

Once consent is executed, the following data should be collected and documented:

- Inclusion and exclusion assessment
- Informed consent
- Enrollment
- Demographics
- Medical history
- Vital signs
- Concomitant medications at time of stroke onset
- Modified Rankin Score (pre-stroke)
- Laboratory evaluations
    - Measurement within 12 hours prior to study administration (if there are multiple measurements, then consider the latest measurement)
        - SOC: aPTT, PT with INR, CBC, platelet count
    - First measurements upon presentation to CPS, within 2-3 hours of study drug administration:
        - SOC: Glucose, creatinine
    - First value collected during hospitalization:
        - SOC: Hemoglobin A1C, Lipid Panel containing total cholesterol, HDL, LDL & triglyceride.
- NIHSS upon arrival to the PCS
- Brain and vascular imaging
- Imagining evaluation findings
- Initial workflow time metrics

17.2 Study Drug Administration

- Time of randomization
- Time of study drug administration
- Research labs:
    - Fibrinogen- processed and resulted at CPS
    - a2AP, MMP-9, and PK studies- processed and frozen. This will be shipped to RCL.
    - Labs must be drawn from a dedicated venipuncture.

- Schedule 30 (±4) Hour Visit

17.3 Post Study Drug 3(±1) hours

- Research labs:
    - Fibrinogen- processed and resulted at CPS
    - a2AP, and MMP-9 and PK studies- processed and frozen. This will be shipped to the RCL.
    - Labs must be drawn from a dedicated venipuncture.

17.4 30 (±4) Hour Visit- Primary Outcomes Visit

- NIHSS assessment by certified and blinded rater
- Research labs:
    - Fibrinogen, PT/INR, aPTT- processed and resulted at CPS
    - a2AP, MMP-9 levels, and PK studies- processed and frozen. This will be shipped to RCL.
    - Labs must be drawn from a dedicated venipuncture.
- SOC labs:
    - CBC
    - Basic metabolic panel- if done as SOC
- Vital signs
- CT/MRI
- CT/MR Perfusion
    - All participants must receive a non-contrast CT scan.
    - If a participant received an MRI at baseline, then they should receive **BOTH** an MRI **AND** CT.
- CTA or MRA (only required if visible vessel occlusion present on baseline imaging)
- Symptomatic ICH
- Major non-ICH systemic hemorrhage
- Clinically relevant systemic hemorrhage
- AEs, SAEs, UEs

17.5 72 Hour Visit/Discharge (±12hrs)

- NIHSS completed by certified and blinded rater
- SOC ani-thrombotics started by end of day 2

17.6 Hospital Discharge

- All concomitant medications administered throughout hospitalization
- Anticoagulant deep vein thrombosis (DVT) prevention dose therapy during hospitalization
- Vascular medications at discharge
- Stroke mechanism – TOAST criteria
- Discharge destination
- Ambulatory status at discharge
- mRS at discharge
- AEs, SAEs, and UEs

17.7 Day 30 (±5) Visit

- Can be completed in person or remote.

- mRS
- NIHSS
- Discharge Summary
- Concomitant medicines
- AEs, SAEs, UEs

17.8 Day 90 (±7) Visit

- Visit should be completed in-person. If in-person is not possible then make all attempts to capture mRS and NIHSS remotely or over the telephone
- mRS
- NIHSS
- Concomitant medications
- Laboratory studies
- AEs, SAEs, and UEs

18.0 Safety Reporting

18.1 Independent Medical Monitor

Dr. Wade Smith, at the University of California, San Francisco is the independent medical safety monitor (IMM) for the study. Dr. Smith will review all serious adverse events in the study as they occur.

The DSMB, after consulting with the study PIs established a plan for how the medical safety monitor will report safety concerns that arise during the trial. The medical safety monitor will attend the biannual meetings of the DSMB and will discuss any concerns about adverse events with the committee.

18.2 Safety Definitions

18.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Site PIs, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

18.2.2 Serious Adverse Events

A serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death,
- is life-threatening,

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994). Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

18.3 Classification of an Adverse Events

18.3.1 Severity of an Event

The severity of AEs and SAEs will be reported using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v5.0) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

CTCAE Severity Grading Summary	
Grade 1:	Mild AE
Grade 2:	Moderate AE
Grade 3:	Severe or Disabling AE
Grade 4:	Life-Threatening AE
Grade 5:	Death related to AE

The complete definitions of these grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

18.3.2 Relationship to Study Drug

The site PI should assess causal relationship between an adverse event and the study drug on the basis of their clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available. The relationship of each reported event to the study drug will be assessed and documented using the following algorithm:

- Not related (must satisfy at least one of the criteria below)
    - Unreasonable or incompatible temporal relationship to study treatment or activities
    - Event is clearly due to extraneous causes (e.g., underlying disease, environment)
- Unlikely (must satisfy at least two of the criteria below)
    - Reasonable or tenuous temporal relationship to study treatment or activities.
    - Could readily have been produced by the subject's clinical state, or environmental or other interventions.
    - Does not follow known pattern of response to study treatment or activities.
    - Does not reappear or worsen with reintroduction of study treatment or activities.
- Possibly (must satisfy at least two of the criteria below)
    - Reasonable temporal relationship to study treatment or activities.
    - Could readily have been produced by the subject's clinical state or environmental or other interventions, but relationship to study participation cannot reasonably be ruled out.
    - Does not follow a known pattern of response to study treatment or activities.
- Probably (must satisfy at least two of the criteria below)
    - Reasonable temporal relationship to study treatment or activities.
    - Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
    - Follows a known pattern of response to study treatment or activities, but a potential alternative cause may be present.
- Definitely (satisfy at least four of the criteria below)
    - Reasonable temporal relationship to study treatment or activities.
    - Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.

- Follows a known pattern of response to study treatment or activities.
- Disappears or decreases with reduction in dose or cessation of study treatment or activities and recurs with re-exposure.

18.3.3 Expectedness

The IMM will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described.

18.3.4 Action Taken Regarding Study Drug

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Increased: The dosage of the study drug was increased.
- Not Applicable: Participant died, study treatment has been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

18.3.5 Other Actions Taken for Event

- None
    - No treatment was required.
- Medication required.
    - Prescription and/or over the counter (OTC) medication was required to treat the adverse event.
- Hospitalization or prolongation of hospitalization required.
    - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other

18.3.6 Adverse Event Outcome

- Recovered/Resolved
    - The participant fully recovered from the AE with no residual effect observed.
- Recovering/Resolving
    - The AE improved but has not fully resolved.
- Not Recovered/Not Resolved
    - The AE itself is still present and observable.
- Recovered/Resolved with Sequelae
    - The residual effects of the AE are still present and observable.

- Include sequelae/residual effects.

- Fatal
    - Fatal should be used when death is a direct outcome of the AE.

- Unknown

18.3.7 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) should always be reported by the PSC within 24 hours of discovery. The NCC will notify the IMM for determination and Translational Sciences, Inc. for communication to the FDA. This is the same process which is outlined below in section 18.4 for SAE Reporting.

The following are considered AESIs:

- Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the criteria of a potential Hy's Law case (total bilirubin level ≥ 2 × upper limit of normal (ULN) with simultaneously ALT or AST ≥ 3 × ULN)
- Symptomatic ICH

18.4 AE/SAE Follow-Up and Reporting

The SAE report should be started in WebDCU™ by the PSC within 24 hours of discovery. The report does not to be fully completed at the time of initial submission. To submit the report, the report will need to be saved and submitted.

The NCC PM will receive an automatic email notification and will follow-up with the CPS, if necessary. The NCC PM will send the SAE report to the IMM for further review. The IMM will review and make a determination. The NCC PM will notify Translational Sciences, Inc. as soon as possible for communication to the FDA.

18.5 Reporting of Pregnancy

The Protocol PI must be notified of any participant who becomes pregnant while receiving study medication after the last dose of study drug. If a female participant partner becomes pregnant within 7 days after the participant receives study medication, the pregnant female partner will be consented so that the pregnancy can be followed through 7 days after birth of the infant. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion, 7 days after birth, to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the site PI, or designee, to report any pregnancy in a female participant or female partners of male participants using the Exposure In Utero (EIU) Reporting form. Please contact the NCC or Prime PM to receive the EIU Reporting Form upon learning of a pregnancy.

The site PI or designee should make every effort to follow the participant until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information,

including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non- serious, should be reported in accordance with study procedures. In case of pregnancy in the female partner of a male patient, the outcome of the pregnancy should be obtained if the female partner agrees. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the site PI should follow the procedures for reporting SAEs outlined in section 17.4.

18.6 Unanticipated Problems

18.6.1 Definition of Unanticipated Events (UE)

The Office for Human Research Protections (OHRP) considers UEs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and

2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Prompt UE Reports to the cIRB also include **any** of the types of events listed below:

- **Risk**: information that indicates a new or increased risk, or a safety issue
- **Harm**: any harm experienced by a participant or other individual that, in the opinion of the investigator is unexpected and at lease probably related to the research procedures
- **Non-compliance**: non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance
- **Audit**: Audit, inspection, or injury by a federal agency
- **Report**: New information from written reports (i.e., study monitors, DSMB, etc.)
- **Research error**: failure to follow the protocol due to the action or inaction of the investigator or research staff.
- **Confidentiality**: breach of confidentiality
- **Unreviewed change:** change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a participant.
- **Incarceration** of a participant in a study not approved by the IRB to involve prisoners.
- **Complaint** of a participant that cannot be resolved by the research team.
- **Suspension**: premature site suspension or termination of the research by the sponsor, investigator or institution
- **Unanticipated** adverse device effect

This definition could include any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the drug, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the drug that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

18.6.2 Unanticipated Event Reporting

Site should report UE as soon as possible. An automatic email will be sent from WebDCU to the NCC PM. The NCC PM will submit a report to the cIRB no later than 10 working days (if it meets the requirements of a prompt report)

The UE report will include the following information:

- Site Name & Subject ID #
- Title of the UE
- Date of the UE and when the date of site first awareness
- Answer questions 06, 07 & 08 – if all three questions are answered "yes" then the UE is to be reported to the cIRB
    - Was this event unexpected?
    - Is this event related or possibly related to the research?
    - Does this event suggest that the research places participants or others at a greater risk of harm.
- Describe the UE in detail.
- Describe the corrective measures the site will use to prevent this UE from happening again.
- Check the type of event. All events except for "OR, The event/deviation/violation does not fit in a category listed above…" require prompt reporting to the cIRB.
- Mark internal event if site is under the cIRB.
- Continue answering the remaining questions, save and submit the form.
- The NCC PM will be notified by automatic WebDCU email that a UE has been submitted by a site.

If the UE meets the definition for the need to report to the cIRB, the NCC PM will submit as "Research New Information" (RNI) to the cIRB, notify the Protocol and Contact PI, Translational Sciences, Inc for FDA communications.

18.7 Interim Monitoring of Events

The IMM will monitor the study with regard to safety on an ongoing basis to identify any safety concerns.

The IMM will review all SAEs and determine whether they are related to study intervention (as described above) and will communicate questions or clarifications regarding an event with the site investigators.

Periodically throughout the study, the Executive Committee and the IMM will review reports on the incidence rates of all reported AEs, whether serious or not. Should such monitoring uncover

issues that may threaten participant safety (e.g., unexpectedly high rate of AEs), the study statistician and PIs will prepare a report to be submitted to the DSMB for their review proposing further actions to be taken, if any.

In addition to monthly Safety Reports, a comprehensive DSMB report will be generated semi-annually by the NDMC: an open report to be distributed to the Executive Committee and MSM, and a closed report to be distributed only to the DSMB. Each semi-annual report will provide cumulative summary statistics on enrollment, participant status in the study, baseline characteristics, protocol violations, safety data (including a summary of the most frequent and most serious AEs, a summary of all MedWatch Reports, and a listing of all participants who were terminated from the study and the reason for termination), and data management/quality information.

The open report statistics will be provided for the overall study with no separation of treatment groups. The closed report will provide cumulative summary statistics by partially blinded treatment group to DSMB members, the NIH liaison, and the project's unblinded statistician. All people with access to the closed reports will be fully independent from trial operation, and have no impact on patient recruitment, treatment, and assessment. If the DSMB wishes to be completely unblinded for these reports, a sealed identification envelope will be provided to the DSMB liaison; this envelope can be opened at the discretion of the DSMB. An annual report will be submitted to the FDA.

19.0 Study Endpoints

19.1 Primary Safety Endpoint

Any ICH visualized on the 30 (±4) h CT scan is the primary study endpoint. This will be determined on the 30 (±4) h CT scan that is uploaded in the central imaging databank by local study personnel, by a trained neuroradiologist who is blinded to the participant's study group assignment.

19.2 Secondary Safety Endpoints

1. Incidence of symptomatic ICH within 30 (±4) h of study drug administration (SITS-MOST definition). (Wahlgren, Ahmed et al. 2007) The presence of type-2 parenchymal hematoma will be determined by a central, blinded, neuroradiologist and a worsening in NIHSS should determine by the NIHSS reported on the study CRF by the local, certified, blinded assessors.
    a. **SITS-MOST Definition**: a local or remote type II parenchymal hemorrhage within 30 (±4) h after treatment (or sooner) associated with a ≥ 4 point deterioration on the NIHSS score from baseline or from the lowest score from baseline to 24 hours, or leading to death.
2. Incidence of non-mICH major or clinically relevant nonmajor bleeding within 30 days of study drug administration.
    a. Non-ICH major bleeding is defined as clinically overt bleeding, that is not ICH, with one or more of the following:
        - Causing a fall in hemoglobin of 2g/dL or more,
        - Or leading to a transfusion of 2 or more units of packed red blood cells or whole blood,

        - Symptomatic and occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra- articular, intramuscular with compartment syndrome, retroperitoneal,
        - Contributing to death
    b. Clinically relevant non-major (CRNM) bleeding is defined as overt bleeding not meeting the criteria for major bleeding that requires medical attention or is associated with discomfort for the participant such as pain, or impairment of activities of daily life.
        - All other overt bleeding episodes not meeting the criteria for major or CRNM bleeding will be classified as nuisance bleeding.
    c. Symptomatic ICH, non-ICH major bleeding, and CRNM will be adjudicated by the study independent medical monitor (IMM)
3. Non-bleeding, SAEs within 90 (±7) days should be determined by direct interview during all study visits.
4. Incidence of stroke-related and all-cause deaths within 90 (±7) days should be determined by direct interview.
5. Plasma fibrinogen levels at 3 (±1) h after completion of T23 therapy should be determined by laboratory testing of study-specific blood draw.

20.0 Study Compliance

20.1 Protocol Deviations and Violations

A protocol deviation is defined as an event where the site PI or site personnel deviate from the study protocol or study procedures. A protocol deviation (PD) may be classified as a protocol violation if a participant's rights, safety or well-being are affected, and/or the completeness, accuracy or integrity of study data is compromised. A protocol violation that impacts patient safety, compromises data integrity or otherwise requires immediate reporting will be classified as a UE. UEs must be submitted through WebDCU™ within 24 hours, excluding weekends/holidays, of site awareness of the event and subsequently reported promptly to the cIRB by the NCC PM.

Protocol deviations will not require immediate reporting. Deviations will be submitted through WebDCU™ as UERs and will be available for site monitoring visits (SMV) and annual reporting at the time of CIRB CR.

CRF data in WebDCU™ should be updated to reflect protocol deviations and violations, when applicable.

Using the UE/PD form within WebDCU™, NCC PM along with the Prime PM will review all entries and determine if a corrective action and preventive action (CAPA) plan is needed for the site. A template CAPA plan document will be provided to the site. The CAPA plan will serve as a contract for corrective and preventive actions and the CCC will follow up with sites to determine effectiveness of the plan.

The site's CAPA will also be submitted with the RNI to the cIRB.

21.0 Data Management

21.1 Data Collection and Study Forms

The most recent version of the SISTER Data Collection Guidelines can be found in WebDCU™ Project Documents. The CRF forms and visit study forms can be found in WebDCU™ via the CRF Collection Schedule.

21.2 Quality Control Procedures

Data quality assurance processes at the NDMC include:

- Logic and rule checks built into the study database.
- Real-time, central monitoring by the data managers and statistical programmers at the NDMC
- Remote and on-site risk-based source verification monitoring by clinical research associates and data managers at the NDMC

21.3 Site Monitoring

The purpose of site monitoring is to ensure that:

- The rights and well-being of human participants are protected.
- Trial data are accurate, complete, and verifiable from source documents.
- The trial is conducted in compliance with the current approved protocol, with GCP, and applicable regulatory requirements.

21.3.1 Scope of Monitoring

- **On-site monitoring**: The monitor will verify specified data entered into the WebDCU™ study-specific database against source documents. Source documents are original documents, data, and records. Examples include hospital records, clinical and office charts, laboratory notes, evaluation checklists, recorded data from automated instruments, x-rays, study worksheets, and eCRFs (in the case of direct data entry). Monitors will query inaccuracies between the source documents and the WebDCU™ database, including the omission of data.

- **Remote monitoring**: Source document verification may be performed remotely by reviewing source documents that have been uploaded into WebDCU™, sent securely to the monitor, or via remote access to electronic medical records (EMR). For SISTER, signed ICFs for participants that are randomized will be uploaded into WebDCU™ and remotely verified by authorized NDMC study team members.

- **Central monitoring**: NDMC staff members will conduct central monitoring using web-based data validation rules, data manager review of entered data and ICD, statistical analysis, and on-going review of site metrics.

21.3.2 Nature and Extent of On-Site Monitoring

The NDMC, in conjunction with the study team, is responsible for determining the number of anticipated on-site monitoring visits, based on the complexity of the study design, its phase of development, previous site experience and compliance with study requirements, rate of participant enrollment, and any other unique attributes of the study and the site. The intensity of site monitoring will be variable across sites. The NDMC is responsible for determining the scheduling of site monitoring visits, including routine, for-cause, and close-out visits based upon risks, as well as determining whether the site visit may be conducted remotely. Remote site

monitoring visits are conducted in the same fashion as on-site visits, except that certain activities may be omitted, such as study drug accountability. The NDMC relies heavily on central monitoring activities to determine when a site monitoring visit is required and to target the work to be performed on-site, in order of priority. The NDMC typically skews site monitoring visits towards the earlier stages of a study so that mistakes are quickly identified, corrected, and alleviated for future enrollments. Upon request from NDMC staff, the site monitor will work with the site to schedule the visit. The objectives of a site monitoring visit will be defined and prioritized by the NDMC prior to the monitoring visit. All work performed, issues identified, and action items by the monitor will be captured via the WebDCU™ monitoring module. Site visits will be conducted by the NDMC as part of routine trial management as well as for cause. At the completion of a site visit the Monitoring report will be available for review and sign-off by the site PI via WebDCU™.

21.3.3 Study Reports

Once the study begins, routine reports prepared by the NDMC will be used to ensure quality control. Reports will be generated to evaluate individual site performance along with overall study performance. These reports will be discussed during the SISTER operations call.

22.0 Data and Safety Monitoring Activates

22.2 Study Halting Rules

The IMM is responsible for ongoing monitoring of reports of SAEs by the clinical centers within 72 hours to ensure Good Clinical Practices (GCP) and to identify safety concerns quickly. The IMM may suggest protocol modifications to the DSMB to prevent the occurrence of particular SAEs, such as modifying the protocol to require frequent measurement of laboratory values predictive of the event or to improve expeditious identification of SAEs.

The NDMC will prepare regular reports concerning SAEs and submit them to the DSMB. In the event of unexpected SAEs or an unduly high rate of SAEs, the IMM will promptly contact the NINDS DSMB liaison, who will notify the DSMB Chair. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for continuing or halting the study to the NIH and the study PIs.

22.3 Confidentiality Policies

These policies define the scope and procedures for the sharing and processing of data from hospitals participating in SISTER.

A Certificate of Confidentiality is granted by the NIH for this trial, in accordance with their policies.

22.3.1 Scope of Data to be Collected

Data associated with participants participating in SISTER:

- CRF data items are specified by the cIRB/IRB/REB approved SISTER protocol. CRF data includes information on assessments, diagnoses, treatments, and medical procedures relevant to stroke specified by the study protocol. Date is the only Protected Health Information (PHI) that is collected on the study CRFs. Date and time for participant enrollment, randomization, study visits, event onset, medical treatments, and clinical procedures are collected during the course of the trial, in order to ensure the trial operation quality and protocol compliance.

- For de-identified data in other media, such as imaging studies and clinical event report files, clinical sites will be instructed to remove PHI (excluding date) from images and files prior to submission to NDMC. These PHI data items are:
    - Names;
    - Date of Birth;
    - All geographical subdivisions smaller than a State;
    - Phone numbers;
    - Fax numbers;
    - Electronic mail addresses;
    - Social Security numbers;
    - Medical record numbers;
    - Health plan beneficiary numbers;
    - Account numbers;
    - Certificate and license numbers;
    - Vehicle identifiers and serial numbers;
    - Device identifiers and serial numbers;
    - Web Universal Resource Locators (URLs);
    - Internet Protocol (IP) address numbers;
    - Biometric identifiers;
    - Full face photographic images and any comparable images; and
    - Any other unique identifying number, characteristic, or code.
- Unredacted singed ICFs will upload into WebDCU™. The PDF file will be linked to the subject ID number but will be stored on a secure server separate from the study's CRF data. The secure server on which these files are stored is not backed up to prevent copies of files containing individually identifiable health information from being copied and stored on non-NDMC back-up servers. The files on these servers can only be accessed by designated study personnel upon entry of a second password. NDMC staff will remotely monitor the informed consent form. Issues identified during monitoring of these documents will be relayed to the CPS for corrective and preventative action. After remote monitoring is complete, the PDF file containing the ICF will be permanently deleted from the secure server. If a participant must be re-consented, the process will repeat itself.

Data associated with participating hospitals and their investigators:

- Regulatory documents required by the cIRB for the participating hospital may include local IRB approval of the study protocol and its amendments, local HIPAA waiver policy, local financial conflict of interest policy, delegation of authority logs.
- Name and contact information of investigators participating in StrokeNet trials.
- Regulatory documents for investigators, including medical licenses, CVs, certifications for performing specific clinical procedures or assessments, financial disclosures, and otherwise.
- Trial operation information, including investigational product (IP) tracking and accountability, public disclosure and community consultation activity reports, investigator trainings, site payments, and otherwise.

22.4 WebDCU™ Data Collection Procedure

All data provided by the participating hospital to the StrokeNet NDMC will be data entered or uploaded by authorized study team members into WebDCU™, the web-based central information management system used for all trials in the StrokeNet.

22.5 WebDCU™ Data Security and Safety Data Protection

WebDCU™ data security and safety are protected by:

- Personal user account and password.
- User permission control based on roles in the study and institutional affiliation.
- Audit trails for data edit.
- Tracking log for user data access.
- Daily differential database backup.
- Weekly full database backup on off-site storage facility.
- WebDCU™ system is hosted at the MUSC Office of the Chief Information Officer (OCIO) Data Center, which is a Tier Level 3 facility covering virus protection, power supply, and natural disaster plan.
- Relational database structure that eliminates data redundancy and discrepancy.
- Logic tier separates the interface and the database, preventing unauthorized access of data in the WebDCU™ system.
- Secure Sockets Layer (SSL) protocol enables encrypted and authenticated communication across the Internet.

After the termination of the study, a public use dataset (PUD) will be created. During this process, a complete de-identification will be performed on all data included in the PUD. Subject IDs and names of clinical sites will be removed. Dates will be transferred from calendar date to number of days from a specified event date, such as randomization or study enrollment. All text fields will be de-identified or removed.

23.0 Study Completion and Closeout Procedures

A site may be closed for many reasons, which include study completion, early discontinuation of the study by the sponsor, or investigator request to discontinue the study at their site. A Site Closeout visit may be completed on-site or remotely, as determined by the NDMC, study team or sponsor and project manager, based on the number of participant enrollments, amount and nature of outstanding items to be monitored, and whether direct access to the participants' electronic medical record has been permitted by the institution.

During the site closeout process, the NDMC Site Monitoring Manager and NCC Project Manager will ensure that all items on the site Close-Out Checklist are completed.

At the completion of the trial, the site staff will need to review the StrokeNet GCP "Onsite Subject Study File SOP" and "Onsite Regulatory Document Checklist SOP". These documents will advise the site regarding the expectations for necessary documentation and retention requirements of trial related information. These documents are in harmony with the Protocol, Trial Expectations, and the StrokeNet Administrative and GCP Policies. When payment for the final participant follow-up is completed, the financial components of the Clinical Trial Agreement will have been met.

24.0 MOP Management

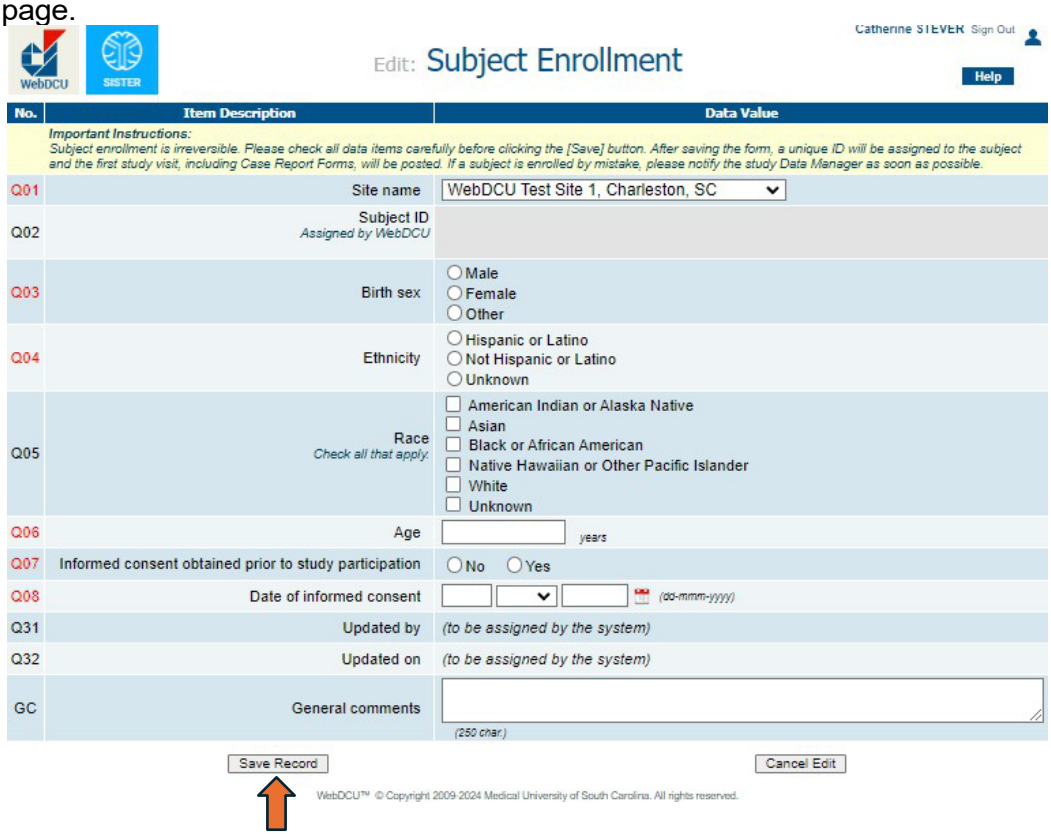
This MOP will be updated throughout the conduct of the study to reflect all study-specific changes. At a minimum, this MOP will be reviewed annually while participants are actively participating in SISTER.

Appendix 1: SISTER Randomization Instructions

SISTER Randomization Instructions:

1. From the SISTER Main Menu screen in WebDCU, click the [Add New Subject] button.

2. Data enter the Subject Enrollment form, then click [Save Record] at the bottom of the page.



3. Once the form is saved, click the green arrow next to 'CRF binder' in Q33 to access the 'Subject CRF Binder'.

6. Data enter, save, and submit F102 Randomization to perform the randomization. Click the green arrow in C05 to access and print the 'Randomization Verification Form' to provide to your site pharmacy. The site pharmacist will then follow their instructions in the Pharmacy MOP for study drug dispensing.