MANUAL OF PROCEDURES

Protocol Version / Version Date
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Protocol Investigators
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Contents

LIST OF ABBREVIATIONS

aPTT	Activated Partial Thromboplastin Time
ADM	Administrative
AE	Adverse event
AIS	Acute Ischemic Stroke
AS	Ancillary Study
AS-PI	Ancillary Study-Principal Investigator
CAPA	Corrective and Preventive Action
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CIRB	NIH StrokeNet Central Institutional Review Board
CITI	Collaborative Institutional Training Initiative
COI	Conflict of Interest
CPS	Clinical Performing Site
CR	Continuing Review
CRA	Clinical Research Associate
CRF	Case Report Form
eCRF	Electronic Case Report Form
CT	Computed Tomography
CTA	Clinical Trial Agreement
CTA	Computed Tomography Angiogram
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CTTI	Clinical Trials Transformation Initiative
DCU	Data Coordination Unit
DM	Data Manager
DOA	Delegation of Authority
DSMB	Data and Safety Monitoring Board
EC	Executive Committee
ED	Emergency Department
EMR	Electronic Medical Record
EOS	End of Study
ET	Endovascular Thrombectomy
ESM	Endovascular Safety Monitor
F&A	Facilities and Administrative
FAQ	Frequently Asked Questions
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subject Protection
ICD	Informed Consent Document
ICH	Intracranial Hemorrhage
ICL	Imaging Core Lab
ICU	Intensive Care Unit
ID	Identification
IMSM	Independent Medical Safety Monitor
IND	Investigational New Drug

IP	Investigational Product
IRB	Institutional Review Board
INR	International Normalized Ratio
ISC	International Stroke Conference
LAR	Legally Authorized Representative
LPI	Lead Principal Investigator
LTC	Lead Trial Coordinator
LTFU	Lost to Follow-Up
LVO	Large Vessel Occlusion
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Score
MUSC	Medical University of South Carolina
NCC	NIH StrokeNet National Coordinating Center
NDMC	NIH StrokeNet National Data Management Center
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OHRP	Office of Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PM	Project Manager
RA	Reliance Agreement
RAR	Response Adaptive Randomization
RCC	Regional Coordinating Center
rt-PA	Recombinant Tissue Plasminogen Activator
SAE	Serious Adverse Event
SC	Study Coordinator
SIV	Site Initiation Visit
SMV	Site Monitoring Visit
SOC	Standard of Care
SOP	Standard Operating Procedure
STIR	Stroke Imaging Research
TNK	Tenecteplase
UCMC	University of Cincinnati Medical Center
UER	Unanticipated Event Report
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others
VTBI	Volume to be Infused

A. STAFF ROSTER

TITLE / ROLE	NAME	CONTACT INFORMATION	WHEN TO CONTACT
Washington University in St. Louis Clinical Coordinating Center (CCC) – Awarded Primary Project Site (PPS)			
Protocol Director / Lead Principal Investigator (LPI)	**Opeolu Adeoye, MD, MS**	Email: adeoye@wustl.edu Phone: 1-833-229-MOST (6678)	· Urgent questions arising during subject enrollment
Responsibility: Will function as the administrative Lead PI. Overall responsibility for the preparation, training and conduct of the clinical trial. Share call duties for questions related to MOST study subjects (Clinical Hotline).			
Lead Trial Coordinator (LTC)	**S. Iris Deeds, MS, CCRP**	Email: irisdeeds@wustl.edu	· Site Training/Initiation · Protocol related questions · Temperature Excursions
Responsibility: Coordination and implementation of on-site study orientation and training of study teams. Ongoing education of coordinators at clinical performing sites. Leads monthly study coordinator calls. Completion and updating of clinicaltrials.gov registration.			
NAME		**CONTACT INFORMATION**	
Other Principal Investigators			
Andrew Barreto, MD, MS		Email: andrew.d.barreto@uth.tmc.edu Phone: 1-833-229-MOST (6678) University of Texas Health Science Center at Houston; Houston, TX	
Responsibility: Will function as the lead recruitment PI for the trial and help to insure protocol adherence. Share call duties for questions related to MOST study subjects (Clinical Hotline).			
Joseph Broderick, MD		Email: broderjp@ucmail.uc.edu Phone: 1-833-229-MOST (6678) University of Cincinnati, Cincinnati, OH	
Responsibility: Will be responsible for facilitating communication within the StrokeNet NCC, RCCs and NDMC. Share call duties for questions related to MOST study subjects (Clinical Hotline).			
James Grotta, MD		Email: james.c.grotta@uth.tmc.edu Phone: 1-833-229-MOST (6678) Memorial Hermann Hospital – Texas Medical Center; Houston, TX	
Responsibility: Will provide expertise regarding the incorporation of other therapies into the management of MOST subjects. Share call duties for questions related to MOST study subjects (Clinical Hotline).			
Colin Derdeyn, MD		Email: colin-derdeyn@uiowa.edu Phone: 1-833-229-MOST (6678) University of Iowa, Iowa City, IA	
Responsibility: Provide guidance and leadership for the initiation and execution of the endovascular aspects of the MOST Trial.			
MOST Clinical (PI) Hotline: 1-833-229-MOST (6678) ***** Questions regarding eligibility or protocol implementation**			
Study Cores			
Independent Medical Safety Monitor (IMSM)	**Steven Levine, MD**		
Responsibility: Review Serious Adverse Events (SAEs) to determine seriousness, relatedness, and expectedness. Review all ICH cases to determine if a hemorrhage is symptomatic.			
Endovascular Safety Monitor (ESM)	**Albert Yoo, MD**		
Responsibility: Review SAE reports to ensure there are no safety issues particular to ET.			

TITLE / ROLE	NAME	CONTACT INFORMATION	WHEN TO CONTACT
MOST Imaging Core Lab (ICL)	**Achala Vagal, MD**	University of Cincinnati	
	Max Wintermark, MD	Stanford University Medical Center	
Responsibility: Cooperatively develop, implement and support the imaging core processes of transferring imaging data securely and perform the centralized interpretation of images. Analysis of particular interest will include, ischemia on baseline imaging as defined by ASPECTS score, baseline vascular imaging assessed for intracranial LVO and safety monitoring for presence of hemorrhage and grading of hemorrhagic transformation on 12-36 hour follow-up imaging.			
Blinded Central Outcomes Adjudication	**Alastair Wilson**	Email: alastair.wilson@glasgow.ac.uk	
Responsibility: Manage video recording upload of 90-day mRS assessment and provide a blinded central read.			
NIH StrokeNet National Coordinating Center (NCC) - University of Cincinnati			
NCC MOST Project Manager	**Melissa Hoffman**	Email: hoffm2ma@ucmail.uc.edu	
Responsibility: Works closely with the CCC Lead Trial Coordinator to determine clinical performing site readiness. Regulatory and performance tracking. Serious and unanticipated Adverse Event (AE) reporting. Liaison between clinical performing sites & IMSM in collection of pertinent clinical information for SAE review. General interaction with NCC, Awarded PRIME Clinical Coordinating Center, NDMC, and clinical participating sites.			
NCC CIRB Liaison	**Susan Roll, RN, BSN, CCRP**	Email: rollsn@ucmail.uc.edu Phone: 513-558-6061	
Responsibility: Processing of CIRB submissions. Annual reviews. Clinical Performing Site Amendments.			
NCC Regulatory Compliance Specialist	**Emily Stinson, MS**	Email: stinsoey@ucmail.uc.edu Phone: 513-558-3979	
NCC Regulatory Compliance Specialist	**Jennifer Golan, MS**	Email: golanjl@ucmail.uc.edu Phone: 513-558-3976	
Responsibility: Regulatory review of clinical performing site documents prior to CIRB submissions. Works closely with the NCC CIRB Liaison, NCC Project Manager, and clinical performing sites study coordinators.			
NCC Contract Specialist	**Wren Hanson**	Email: hansonwm@ucmail.uc.edu Phone: 513-558-6566	
NCC Contract Specialist	**Eileen O'Shaungnessy**	Email: oshaugen@ucmail.uc.edu Phone: 513-558-3924	
Responsibility: Assist the Contract Manager with the StrokeNet legal agreements and compliance documentation needed for the StrokeNet network and the various clinical trials.			
NCC Financial Management		Email: strokenettrialpymts@ucmail.uc.edu	· Reporting, budgeting, per-subject payment questions or remittance instructions
Responsibility: Budgeting, grant expense monitoring and reporting. Initiate invoices for payment using WebDCU™ payment module.			

TITLE / ROLE	NAME	CONTACT INFORMATION	WHEN TO CONTACT
NCC Central Pharmacy		Email: strokenetcpharm@ucmail.uc.edu Phone: 513-584-3166	· Study Drug shipment, handling and maintenance
NIH StrokeNet National Data Management Center (NDMC)			
WebDCU™ Emergency Randomization Hotline 1-866-450-2016 *****Call if experiencing problems with performing randomization**			
StrokeNet NDMC Project Manager	**Jessica Griffin, CCRP**	Email: simonsjl@musc.edu Phone: 843-792-1677	· WebDCU™ user account set-up
MOST Trial WebDCU™ Data Manager	**Jocelyn Anderson, MPH**	Email: anderjoc@musc.edu Phone: 843-876-1167	· WebDCU™ user account set-up · Data management questions
MOST Trial WebDCU™ Data Manager	**Rebecca Harrison, MPH**	Email: harrisre@musc.edu Phone: 843-876-1262	· WebDCU™ user account set-up · Data management questions
MOST Site Monitoring Manager	**Katherine Trosclair, MPH**	Email: trosclak@musc.edu Phone: 843-792-3980	· Site monitoring questions . Informed consent questions

B. STUDY ORGANIZATION AND RESPONSIBILITY

1. National Institute of Health (NIH) StrokeNet National Coordinating Center (NCC) - University of Cincinnati

The NIH has created the NIH StrokeNet NCC to conduct small and large clinical trials and research studies to advance acute stroke treatment, stroke prevention, and recovery and rehabilitation following stroke. This network of 24 regional centers plus 5 legacy regional centers across the U.S., which involves more than 300 hospitals, is designed to serve as the infrastructure and pipeline for exciting new potential treatments for patients with stroke and those at risk for 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 (PI) and his/her team to manage trials within the NIH StrokeNet.

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

1.1 NCC Project Manager

Overseeing the MOST team is the Project Manager (PM) who coordinates with the Trial Protocol PIs and Lead Trial Coordinator (LTC) as well as the CIRB and National Data Management Center (NDMC). The responsibilities include but are not limited to the following services: provides review via WebDCU™ of all clinical performing site (CPS) study staff credentials and essential documents; performs initial review of acuity and completeness of reported serious adverse events (SAE) requiring Independent Medical Safety Monitor (IMSM) review; verifies that contractual and regulatory requirements are finalized prior to NCC authorization of the CPS to begin active recruitment; maintains communication with NCC, Prime Awarded Project PI and LTC, NDMC and participating CPSs; and, verifies study site payments with NCC financial manager.

1.2 NCC Contract Specialists

The NCC Contracts Specialists prepare and execute the MOST Clinical Trial Agreement (CTA) for both the network and non-network CPSs. The CTA contains a fixed cost per study site payment budget, a special National Institute of Neurological Disorders and Stroke (NINDS) approved Facilities and Administrative (F&A) rate, a Standard of Care (SOC) document and any special terms and conditions associated with trial recruitment and payment. Each participating network hospital signs a Reliance Agreement (RA) with the University of Cincinnati that delegates the responsibility of human subject protection review to the StrokeNet CIRB at the University of Cincinnati.

1.3 NCC Financial Management

Study sites will not submit invoices to pass-through entity for study activities completed. The NCC Financial Management team will issue startup payments and subject enrollment reimbursements based on data entry and imaging transmission flags within the NDMC WebDCU™ payment module. Payments for startup, subject enrollment and interval/milestone achievement, as outlined in the Payment Schedule (see the following URL: https://www.nihstrokenet.org/most/resources), will be made no less than quarterly for all tasks confirmed as completed by NCC Contracting (startup funds inclusive of full execution of the CTA and CIRB approval of Study Start-Up), or by NDMC (study-related reimbursements). Deductions from payments are made for missing data as stipulated in the Payment Schedule. Subject reimbursements are inclusive of F&A costs. Payments are to be made via electronic funds transfer. Payments will be sent only after remittance instructions have been received and accepted by Accounts Payable. For information about electronic funds transfer please contact the Financial Management team.

1.4 NCC Central Investigational Review Board (CIRB) Liaison – University of Cincinnati

The StrokeNet CIRB at the University of Cincinnati is the trial protocol CIRB of record for all participating CPSs. Each CPS is required to have an active current Federalwide Assurance (FWA) and executed RA in place. The CIRB liaison works with the LTC, NCC PM, NCC Regulatory Specialist, CPSs and WebDCU™ on regulatory document compliance, developing and approving the informed consent, foreign language full consents, Health Insurance Portability and Accountability Act (HIPAA) authorization, protocol amendments, unanticipated event reports, approval of study related documents, and annual/continuing review (CR). The CPS IRBs remain in close communication with the CIRB to provide knowledge of the local research context.

1.4.1 NCC Regulatory Specialist

Provides regulatory review via WebDCU™ of all regulatory documents; compiles CIRB submission materials and CR documents from CPSs, and when complete, provides submission documents to the CIRB for review/approval; processes CIRB queries and/or approvals to CPSs.

1.5 NCC Central Pharmacy – University of Cincinnati

The NIH StrokeNet NCC Central Pharmacy will be responsible for all aspects of investigational product management and distribution for all drug studies within the StrokeNet.

The Central Pharmacist must meet 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

1.5.1 NCC Central Pharmacist / NCC Central Pharmacy Technician

Prepares and dispenses investigational study drug kits materials issued through the NCC Central Pharmacy. Manages required record-keeping, shipping, ordering, and inventory activities. Ensures the accuracy and integrity of products prior to their delivery to trial CPSs. 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, Federal Drug Administration (FDA) regulations and legal requirements for pharmacy operations. The NCC Central Pharmacy will provide Study Drug Dispensing Guidelines that will summarize: patient enrollment and randomization, study drug and Activated Partial Thromboplastin Time (aPTT) ordering, drug assignment and dispensing, and site pharmacist or designee responsibilities for the CPS pharmacy. These guidelines are designed to allow a pharmacist to dispense an investigational drug 24 hours a day. In addition, the MOST Clinical Performing Site Study Drug Procedure document will provide the protocol's purpose, design, pharmacology, dosage and administration guidelines, preparation, blinding, labeling, and documentation requirements.

The NCC Central Pharmacist oversees the work performed by the NCC Central Pharmacy Technician(s) and identified staff to ensure that performance standards are maintained and that work is accurate and in accordance with state, federal and organizational regulations.

2. Washington University in St. Louis Clinical Coordinating Center (CCC)

Dr. Opeolu Adeoye is the NIH Awarded PI for the primary project site at Washington University in St. Louis. Responsibilities of the Washington University in St. Louis CCC include but are not limited to identification of CPSs, CPS training, overall trial recruitment, serving as a resource to the CPSs for questions regarding inclusion/exclusion criteria, and protocol implementation and compliance.

2.1 Lead Principal Investigator (LPI)

The MOST Trial Protocol was developed and will be maintained by Dr. Opeolu Adeoye at Washington University in St. Louis. Responsible for intellectual leadership for the study protocol, overall conduct of the trial and protection of participant safety. Maintains compliance with applicable law and regulations, and serves as the director of trial operations.

2.2 Lead Trial Coordinator (LTC)

Overseeing the Washington University in St. Louis CCC MOST team is the protocol sponsor LTC who coordinates with the NCC PM as well as the CIRB and NDMC. Responsibilities include but are not limited to the following services: acting as the primary point person for all Data and Safety Monitoring Board (DSMB) correspondence, maintains FDA protocol correspondence on behalf of the sponsor, sends trial updates and urgent notifications to sites, maintains ongoing communication between Washington University in St. Louis CCC, NCC and NDMC, documents and manages site training at participating CPSs, and coordinates communication on behalf of the trial. Assists the Protocol PI with preparation, submission and maintaining FDA reports and correspondence.

2.3 MOST Imaging Core Lab (ICL)

The ICL will receive all neuroimages performed within 72 hours of symptom onset. Within 12-36 hours of baseline, all participants will have a SOC follow-up computed tomography (CT) or magnetic resonance imaging (MRI) based on the Stroke Imaging Research (STIR) consortium recommendations, which will be interpreted for evidence and classification of intracranial hemorrhage (ICH). All images (baseline and follow-up) will be uploaded to WebDCU™ by the CPS. Baseline CT/CT angiography or MR/MR angiography images will be reviewed by the ICL central readers for ASPECTS score (CT), site of large vessel occlusion (LVO) and collateral status. Follow-up imaging studies will be reviewed for possible hemorrhagic complications and infarct volume. ICL personnel will be blinded to clinical data and treatment assignment with discrepancies resolved by consensus.

Refer to the MOST Imaging Core Lab Manual document for detailed imaging data transfer instructions located in WebDCU™ under “ToolBox”→”Project Documents”.

3. StrokeNet National Data Management Center (NDMC) – Medical University of South Carolina (MUSC)

The NDMC is the centralized data management center for the NIH StrokeNet. MOST data management, site monitoring, interim data analysis and statistical reports, tracking of neuroimaging and unblinded interactions with the DSMB are conducted by the NDMC at the Medical University of South Carolina (MUSC). The NDMC has created the MOST database and developed the interface to the web-based clinical trials management system (CTMS), WebDCU™ (https://webdcu.musc.edu/login.asp), where CPSs personnel randomize patients and enter data into the electronic case report forms (eCRFs). MOST data will be shared in accordance with the StrokeNet data sharing policies and in compliance with federal requirements.

4. Clinical Performing Sites (CPSs)

Up to 110 CPSs are proposed in the MOST protocol. 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. In addition, MOST study team members may include sub-investigator(s), study coordinators, a CPS pharmacist and other qualified study staff who will be responsible for enrolling the participants and collecting the data for this trial.

5. The University of Glasgow

The University of Glasgow will provide the management of a centralized adjudication system for the blinded scoring of a video-recorded assessment of the 90-day modified Rankin Score (mRS). The

centralized scoring will serve as the primary outcome for the trial and will be compared against the local mRS. The University of Glasgow will develop training tools to cover technical aspects of the video upload system, ongoing technical support and provide the video recorder to the CPSs.

6. Study Committees / Cores

6.1 MOST Executive Committee (EC)

The EC will provide overall clinical guidance and leadership for the execution of the MOST Trial. The EC will oversee study conduct, protocol compliance and modifications, and basic reports generated to monitor and guide the study. Responsibilities include oversight of the overall conduct of the study with regard to protocol compliance and modifications/amendments, study progress, and problem solving. This committee will provide a means of partnership between the investigators, NINDS, and the sponsors. The EC, composed of experts in emergency medicine, vascular neurology, endovascular therapy and neuroimaging, and biostatistics will provide the overall scientific guidance for the study. The EC will be co-chaired by the LPI, Dr. Opeolu Adeoye, and PI, Dr. Andrew Barreto. The committee will meet quarterly by phone (1 hour/quarter) for the full duration of the study

After the database is locked, this committee will become the MOST Trial Publications Committee. The Publications Committee will participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

6.2 Eligibility Core

The eligibility core will function to provide oversight for the urgent / time sensitive questions pertaining to the assurance of appropriate randomization of screened patients. The Core will coordinate the 24/7 coverage of the MOST Clinical Hotline: 1-833-229-MOST (6678). The MOST Clinical hotline is available for consultation on screening, eligibility, and randomization questions. This number will be staffed by one of the MOST Trial PIs at all times.

Appropriate categories of issues that might lead to hotline calls might include, but may not be limited to, questions regarding eligibility criteria, study procedures, adverse events (AEs), outcomes, or emergency medical issues. The emergency medical issues might include the need for unblinding due to an adverse bleeding event or the need for urgent surgery. Via WebDCU™, the Core will receive regular updates that will include numbers of participants consented and randomized, and number of participants that are eligible but not consented.

6.3 Imaging Core

The Imaging Core will cooperatively develop, implement and support the processes of transferring imaging data securely and performing the centralized interpretation of images.

6.4 Outcomes Core

The outcomes core will troubleshoot issues regarding the video upload and central adjudication processes.

6.5 Pharmacy Core

The pharmacy core will provide guidance for study drug handling, preparation and shipment. Inventory of study drug as it relates to response adaptive randomization (RAR) will also be managed by the pharmacy core.

7. Independent Medical Safety Monitor (IMSM)

The blinded IMSM will review all SAE reports submitted by the CPSs throughout the trial and will determine if reported ICHs are symptomatic. He/she will also be responsible for ensuring good clinical practice (GCP) and to identify safety concerns reportable to the FDA. The IMSM may suggest protocol modifications to prevent the occurrence of particular AEs, e.g., modifying the protocol to require frequent measurement of laboratory values predictive of the event or to improve expeditious identification of SAEs. To minimize bias, he/she will evaluate SAEs blinded to treatment assignment, unless the DSMB approves partial or complete unblinding. In the event of unexpected SAEs or an

unduly high rate of SAEs, the IMSM will promptly contact the LPI and the NINDS Program Official who will notify the DSMB Chair. The IMSM will also have final say in adjudicating all other safety outcomes.

8. Endovascular Safety Monitor (ESM)

The blinded ESM will review all SAE reports submitted by the CPSs that involve endovascular thrombectomy (ET) to assess safety particular to ET. He/she will ensure there are no safety issues reportable to the FDA particular to ET [performance by individual interventionists or sites]. The ESM may suggest protocol modifications to prevent the occurrence of particular AEs, e.g., modifying the protocol to require frequent measurement of laboratory values predictive of the event or to improve expeditious identification of SAEs. To minimize bias, he/she will evaluate SAEs blinded to treatment assignment, unless the DSMB approves partial or complete unblinding. In the event of unexpected SAEs or an unduly high rate of SAEs particular to ET subjects, the ESM will promptly contact the LPI and the NINDS Program Official who will notify the DSMB Chair.

9. Data and Safety Monitoring Board (DSMB)

This independent committee will determine at study initiation whether to review blinded or unblinded data, will perform data reviews and analyses at regularly scheduled intervals, will be responsible for final determinations of safety and ethical concerns, recommendations about whether the study should continue, and other related issues. The DSMB will also have access to the IMSM who will review AEs on an ongoing basis. The members of the DSMB have been chosen by the program staff at NINDS and will not include any of the PIs or members of the study team.

C. TRAINING PLAN AND REGULATORY MAINTENANCE

The goal of training is to ensure human subjects protection and a full understanding of the protocol, as well as to standardize the methods of data collection to help ensure comparability of data across sites. Prior to the activation of any CPS, the training requirements outlined in this section must be completed and uploaded to the regulatory documents tab in WebDCU™. When new study personnel join during the trial, they must complete the on-line training via the WebDCU™ training site (https://webdcu.musc.edu/campus/) and upload all required training documentation prior to participating in any study related activities.

1. WebDCU™ Navigation

In order to set up initial personal WebDCU™ login credentials during study startup, contact the MOST WebDCU™ Data Managers. For all new study team members who join after the study is started, the Add New Study Team Member Form can be filled out in WebDCU™. All MOST study personnel will be provided with a username and temporary password for the purpose of accessing WebDCU™. The link to the WebDCU™ database is: https://webdcu.musc.edu/login.asp. You will be prompted to change your temporary password the first time you log on to WebDCU™. 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, "MOST → 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
- MOST Regulatory Document Parameter Guidelines for WebDCU™
  - Contains instructions specific for posting study required documents
- MOST Data Collection Guidelines
  - Contains general and specific guidelines for completion of MOST CRFs
- MOST Randomization Instructions
- MOST Manual of Procedures (MOP)
- MOST Enrollment Tools
- MOST CPS Study Drug Procedures
- MOST Participant Correspondence Letters

MOST-specific training modules are located at (https://webdcu.musc.edu/campus/ - Project Specific Training → MOST Project). Another way to access the project specific training for MOST is located on the WebDCU™ login page located at https://webdcu.musc.edu/login.asp. At the bottom of the page is a link for WebDCU™ Training Center. By clicking on this link, you will be routed to the WebDCU™ Training Center page. See sections 5-7 below for details on required training modules.

2. Human Subjects Protection (HSP) and GCP Training

It is the expectation that all investigators and staff involved in the conduct, oversight, or management of this NIH funded trial must be trained in and comply with all local, and US federal requirements for the initiation and ongoing performance of a clinical trial per the principles of GCP as defined in International Council for Harmonization Consolidated Guidance (ICH E6) and Title 45 and part 46 Federal Policy for the Protections of Human Subjects "Common Rule". Acceptable documentation of GCP and HSP will be a training module from an accredited institution that describes the investigational nature of the MOST Trial.

Participating institutions may require a particular program (e.g. Collaborative Institutional Training Initiative [CITI] Training) or may choose to develop a program to meet these requirements. Frequency of HSP and GCP training is institution specific and will be driven by the expiration date stated on the certificate. If no expiration date is listed and if not in conflict with local institutional policy, the expiration

date is 3 years from the certification date. All study staff members are required to have undergone HSP and GCP Training, as determined appropriate by your institution for fulfilling this education requirement, prior to participating in the MOST study. Documentation of training must be uploaded to WebDCU™ and verified initially by the NCC Project Manager and then by the StrokeNet CIRB prior to initial site approval and when adding new study personnel.

3. CIRB

All Regional Coordinating Centers (RCCs) and Satellites, which includes CPSs, have signed a StrokeNet CIRB Reliance Agreement prior to being trial eligible. Use of the StrokeNet CIRB is NIH mandated.

Process Overview:

1) Prime Award Site PI will submit the protocol and Informed Consent Document (ICD) template (along with any other study-wide documents that need CIRB approval) to the NCC Project Manager for submission to the CIRB. All approved documents will then be available for distribution to the performance sites.
2) The NCC Project Manager and NCC Regulatory Specialist will work together to distribute to the CPS the following documents:
    a. Prime Protocol Approval Letter
    b. Approved Prime Protocol
    c. Any approved Study-Wide Documents
        i. MOST Participant Study Information Sheet
        ii. Lost To Follow-Up (LTFU)
    d. ICD Template
    e. ICD Instructions
    f. Stand-alone HIPAA Authorization Form
    g. Performance Site Application Form
    h. CIRB Assurance Form (to be completed by only Site PI)
    i. Local Site Context Form (to be completed in conjunction with the performance site's local Human Subjects Protection Program or equivalent office)
    j. Partial HIPAA Waiver Request for screening purposes
    k. Financial Conflict of Interest (fCOI) Form
3) The CPS CIRB Application Packet (inclusive of the documents noted above) will be reviewed by the NCC Regulatory Specialist for completeness prior to submission to the CIRB.
4) Upon receipt of CIRB approval, the NCC Regulatory Specialist will upload to WebDCU™ the approval letter, and approved documents (ICD, MOST Participant Study Information Form and Stand-alone HIPAA Authorization Form) before distributing all approved documents to the CPS.

For CIRB submissions, follow the study specific directions provided by the NCC PM and NCC Regulatory Specialist in the MOST Study Start-Up email.

Following is a chart that breaks down CIRB Responsibility versus Local Site Responsibility:

CIRB Responsibility	Local Site Responsibility
IRB review tasks ➢ Initial review ➢ Continuing review ➢ Amendments, deviations, etc. ➢ COI	**Site specific context** ➢ Local laws ➢ Institutional policies ➢ Local context ➢ COI
HIPAA determinations of: ➢ Authorization forms and any accompanying request for alterations when authorization is combined with informed consent ➢ Requests for waivers of authorization	**Ancillary reviews** ➢ Nursing ➢ Radiation ➢ Safety
Local context review ➢ Collect local information required for IRB review ➢ Distribute a high-level protocol synopsis and highlights sheet	**Other compliance areas** ➢ HIPAA requirements outside those expressly covered by CIRB ➢ Oversight of research conduct ➢ Other required reporting and actions under federal, local, or institutional laws, regulations or policies

4. Form FDA 1572

The sponsor is required to obtain a signed investigator statement (Form FDA 1572) for each CPS before permitting the site to begin MOST activities. This Form FDA 1572 provides the sponsor with CPS information, investigator qualifications and informs the investigator of his or her obligations to follow FDA regulations. CPSs must provide the sponsor with a Form that lists all active, critical research personnel and the CPS must provide updated Forms as personnel are added or removed from their team. It is necessary to list the PI, sub-Is, research coordinators, and any person performing critical study functions such as collecting and evaluating study data.

5. MOST Required Training

PIs, sub-investigators, study coordinators, and other study personnel must show evidence of training in the protocol and study procedures, eligibility requirements, CRF completion, and WebDCU™ procedures, as applicable. Protocol training will be conducted by the MOST CCC at Washington University in St. Louis in any of the following manners: Protocol Specific Webinar(s), Site Initiation Visit (SIV), Site Readiness Call, and Investigator Meeting. Training will be verified by a meeting sign-in sheet, or attestation form, which will serve as the documentation of training for posting in WebDCU™.

For those not able to attend in-person protocol training, web based training modules located on the MUSC-supported training WebDCU™ at https://webdcu.musc.edu/campus/ may be completed instead. After viewing the training module(s), individuals will complete the corresponding training test(s) and upload the email generated certificate to the regulatory file in WebDCU™ prior to their approval to participate in study activities. The addition of any newly added study personnel will need to follow the same training procedures prior to conducting any study related activities.

5.1 Protocol Training

Protocol Training covers the following objectives:

- Study objectives
- Inclusion/Exclusion criteria
- Eligibility requirements
- Randomization and assignment of Study Drug Kit ID
- Laboratory evaluations
- Study drug administration and argatroban titration protocol
- Prohibited concomitant treatments
- Subject assessment schedule
- Subject visit schedule
- Safety monitoring

Each individual responsible for completing Protocol Training is required to complete the associated Protocol Training Test. Once the individual achieves a passing score of at least 80%, a training certificate will be sent directly to that individual via email. The email must be saved as a PDF and uploaded to the regulatory file in WebDCU™.

5.2 Study Coordinator Training

Study Coordinator Training covers the following objectives:

- ICF upload to WebDCU™
- Imaging file upload to WebDCU™
- 90-day mRS video recording and upload to University of Glasgow CARS Portal

Each individual responsible for completing Study Coordinator Training is required to complete the associated Study Coordinator Training Test. Once the individual achieves a passing score of at least 80%, a training certificate will be sent directly to that individual via email. The email must be saved as a PDF and uploaded to the regulatory file in WebDCU™.

5.3 Pharmacy Training

Pharmacy Training covers the following objectives:

- Study drug receipt, handling and storage
- Randomization and assignment of Study Drug Kit ID
- Study drug reconstitution and dispensing

Each individual responsible for completing Pharmacy Training is required to complete the associated Pharmacy Training Test. Once the individual achieves a passing score of at least 80%, a training certificate will be sent directly to that individual via email. The email must be saved as a PDF and uploaded to the regulatory file in WebDCU™.

5.4 NIH Stroke Scale Certification (NIHSS)

The protocol required NIHSS assessments should be completed by a qualified MOST study team member who has a current NIHSS certification and is assigned that responsibility on the Delegation of Authority (DOA) Log. However, the NIHSS assessor may be an undelegated person if the NIHSS is being collected as part of routine clinical care. It is best practice for study team members to confirm a clinical assessment that is used for research purposes.

Recertification will be required as per the stated expiration date on the certificate. If no expiration date is specified, 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. Guidelines for performing the NIHSS assessment can be found in WebDCU™ (Toolbox → Project Documents → MOST Data Collection Guidelines) and resource link for NIHSS training certification can be found at https://webdcu.musc.edu/campus/). Upon completion of the web based training module, the

corresponding course completion certificate must be printed off and posted in the CPS regulatory file in WebDCU™ prior to initial site approval to enroll.

5.5 modified Rankin Scale Certification (mRS)

The protocol required mRS assessments should be completed by a qualified MOST study team member who has a current mRS certification and is assigned that responsibility on the DOA Log. However, the baseline mRS assessor may be an undelegated person if the mRS is being collected as part of routine clinical care. It is best practice for study team members to confirm a clinical assessment that is used for research purposes. The 30 and 90-day mRS assessor must be on the DOA Log.

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. Guidelines for performing the mRS assessment can be found in WebDCU™ (Toolbox → Project Documents → MOST Data Collection Guidelines) and mRS training certification can be obtained at https://webdcu.musc.edu/campus/). Upon completion of the web based training module, the corresponding course completion certificate must be printed off and posted in the CPS regulatory file in WebDCU™ prior to initial site approval to enroll.

5.6 Informed Consent Requirements

All study personnel designated on the DOA Log with the responsibility of obtaining informed consent on behalf of the trial must document acceptable GCP and HSP Training. Only study personnel who have been approved as delegated and trained may obtain informed consent for MOST.

6. On-going Training Efforts

Annual Investigator meetings and/or other study identified meetings, will offer further opportunities for protocol training, to give trial updates, re-train and educate, address problems or concerns, and generate continued enthusiasm for the trial. MOST protocol retraining will occur if a CPS has greater than or equal to 6 months with no randomizations. Personnel from the CCC, NCC and the NDMC will be available to provide any assistance or training that may be required or requested. The Protocol, Manual of Procedures (MOP), Regulatory Document Parameters Guidelines and other study-specific documents are available on the MOST WebDCU™ website under “ToolBox”→”Project Documents”.

6.1 6-Month Protocol Retraining

If a site goes without any randomizations for a 6-month time period, the MOST Leadership team will schedule a conference call with the site PI and lead study coordinator to discuss site-specific barriers to enrollment and create solutions. In addition, site personnel are encouraged to review the protocol, MOP and Frequently Asked Questions (FAQ) when lapses in site activity occurs.

7. Required Training

Please refer to the MOST Regulatory Document Parameter Guidelines document that is located under “ToolBox”→”Project Documents” for an outline of site-wide and individual study team member training requirements that should be uploaded to the regulatory documents tab on the MOST WebDCU™ website.

D. COMMUNICATIONS PLAN

Ongoing study communication will be maintained through, but not limited to, the following mechanisms for the duration of the trial:

1. MOST Clinical Hotline: 1-833-229-MOST (6678)

The MOST Hotline is a toll free number to be used for urgent / 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.

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.

3. DSMB Meetings

The MOST DSMB met prior to final study approval and study initiation and will continue to meet semi-annually or on an as needed basis dependent on enrollment and safety findings throughout the duration of the trial. Participant organization for these meetings is in coordination with NIH/NINDS staff.

4. Investigator Meeting

The MOST trial will include up to 110 sites. There will be an Investigator Meeting held at the beginning of the study that will include a PI and Study Coordinator (SC) from each CPS. This meeting will serve as the initiation and protocol training for all CPS investigators and SCs who are able to attend.

At least one additional investigator meeting will be held during the course of the study and is usually held at the time of study closeout. Shorter investigator meetings, or other study identified meetings, will be held annually to coincide with the International Stroke Conference (ISC) to offer further opportunities for protocol training and to give trial updates. Personnel from the Washington University in St. Louis CCC, the NCC and NDMC will be available to provide updated study information and training that may be required or requested.

5. StrokeNet Website and ClinicalTrial.gov

MOST has a dedicated website that can be accessed directly at https://nihstrokenet.org/most. The NIH StrokeNet website contains information for both healthcare professionals and laypeople and is maintained by the StrokeNet NCC.

The MOST trial is listed on ClinicalTrials.gov, NCT03735979. Any changes, updates and results are maintained by the Washington University in St. Louis CCC Trial Sponsor, or the CCC Lead Trial Coordinator.

6. Investigator Webinars

Investigator Webinars occur at least quarterly via teleconference on pertinent topics of interest or identified need. The Washington University in St. Louis CCC and the NCC Project Manager jointly organize and facilitate these calls. The presentation slides and meeting recordings are available at https://nihstrokenet.org/most/webinars.

7. MOST Steering Committee Calls

The MOST Steering Committee will form by the end of the first year that the study is open for enrollment. This group of site PIs and/or designees will typically meet quarterly or as needed by phone for the full duration of the study to discuss the overall conduct of the study with regard to protocol compliance, modifications/amendments, study progress, problem-solving and other issues pertinent to ensure the ongoing success of the study.

8. MOST Trial Operations Calls

Weekly trial operations updates are provided to the NIH StrokeNet Operations Committee with meeting agenda and minutes distributed by the NCC.

9. Webinars / Teleconferencing

The NCC Education Coordinator organizes monthly webinars and agendas are sent in advance to all RCC and CPS coordinators.

10. Site Directory

The MOST site directory is maintained within WebDCU™. Each CPS is responsible for notifying the MOST Project Manager whenever there is a change to key site personnel (e.g., PI, primary study coordinator) and updating the DOA Log in WebDCU™ as appropriate.

11. Newsletters

The MOST study team issues newsletters via email at least monthly. These trial newsletters will contain enrollment updates, identified common problems and potential solutions, important reminders, and information on upcoming events (webinars and training).

12. Additional Communications

Additional communications will be conducted on an as-needed basis for team building, sharing success strategies, training and discussion of any pertinent issue or identified need. For study team contact information and who to contact for specific questions, please see the Staff Roster, MOP Section A.

E. RECRUITMENT PLAN

Recruitment is the dialogue which takes place between an investigator and a potential participant/Legally Authorized Representative (LAR) prior to the initiation of the consent process. It begins with the identification, targeting and enlistment of participants for the research study. Up to 1,200 Acute Ischemic Stroke (AIS) patients meeting the pre-defined inclusion and exclusion criteria will be enrolled in the trial at up to 110 sites. The MOST team will assist in the recruitment process by developing a close working relationship with participating sites. This relationship will include training, correspondence, conference calls and site visits.

The site PI, SC and other qualified support staff will have a process in place for screening all potential research study participants (including overnight, weekends and holidays). Participant recruitment includes ongoing collaboration with the hospital Stroke Team, Emergency Department (ED) physician(s), fellow(s) and resident(s) so subjects may be identified as potential MOST candidates as early as possible during their encounter for an AIS. Given the acuity of this protocol, coordination between the research and clinical teams will be crucial in order to enroll patients and start study procedures expediently and within the outlined time window. Identification will likely occur in the ED therefore it is important to have a system in place for early notification of the research team. It is expected that the site PI and study staff will educate the Emergency Medicine and Stroke Teams at their participating CPSs on the MOST interventions, protocol synopsis, inclusion/exclusion criteria and instructions to promptly notify the research team of any potentially eligible patients.

To help maximize identification of AIS patients the following is recommended:

- ED education of physicians, nurses and resident/fellow staff
- Stroke Team education of physicians, nurses and resident/fellow staff
- Grand rounds presentation (MOST training module slides are available to the sites)
- MOST laminated inclusion/exclusion criteria pocket cards distribution
- Outreach to specialty nursing units (Intensive Care Unit [ICU], Step-down units, etc.)

Trial enrollment will be tracked using the study progress module in the WebDCU™ for comparison to the NINDS recruitment plan. The operations team will monitor CPS-specific recruitment. Screen failure reports will be reviewed to identify recruitment issues or shortcomings. The CCC and the NCC will assist sites in problem solving recruitment issues in an effort to help identify methods that may increase enrollment, tailoring it to specific sites when possible.

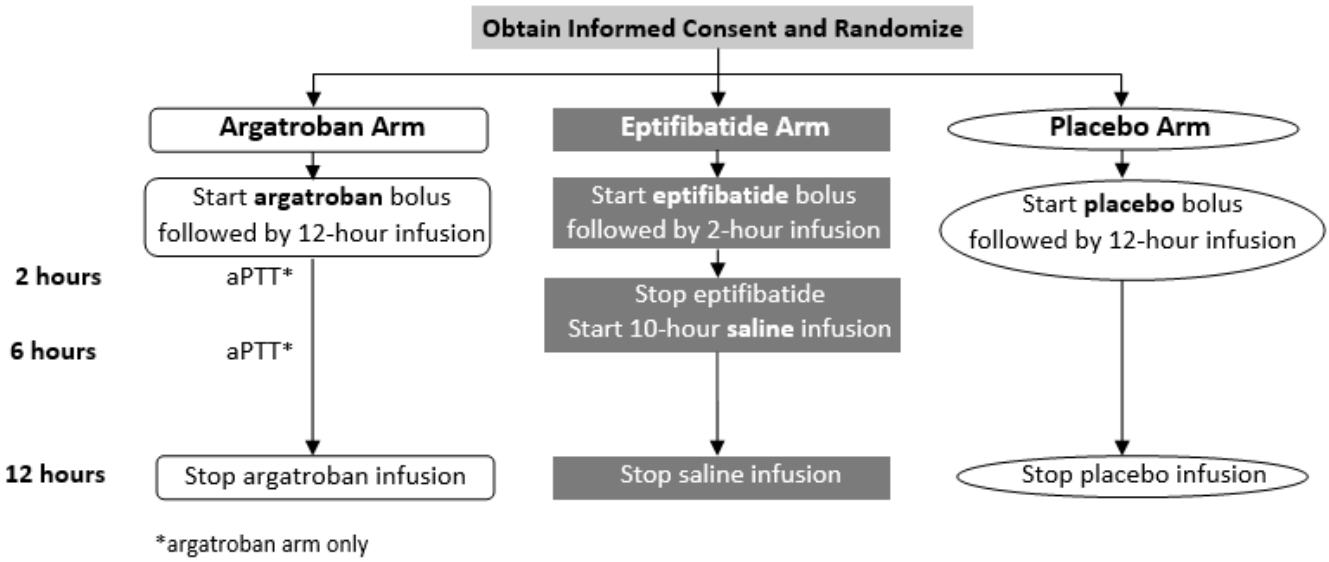
F. RETENTION PLAN

Once a patient is randomized into the study, the CPS will make every effort to retain them through the 90-day follow-up to minimize possible bias associated with LTFU. Steps to help ensure research study participants will complete their 30 and 90-day visits within the allowable visit window include but are not limited to the following:

- Ensure participant contact information is correctly recorded and the number is still in use at the time of enrollment. If the contact information collected is not the participant's, verify the identity of the person and their relationship with the participant. Attempt to get at least two contact numbers/alternative contact information for each participant (e.g., home, mobile, email address), as one contact number may not be adequate or always in service.
- Call or send reminders for upcoming visits and accommodate participant's schedule as much as possible while staying within the MOST trial event window.
- If the participant cannot be contacted via telephone to complete the 30-day study visit, every attempt should be made to complete the mRS in-person if the participant is being seen at the study hospital for another visit within the 30-day time window.
- If the participant is unwilling or unable to return to the study site to complete the 90-day study visit in person, every attempt should be made to accommodate a face-to-face interview for the purpose of obtaining the required video-recorded mRS. Possible alternate 90-day visit arrangements outside of the clinic or study site are, visits to the healthcare facility where the participant may be residing and in-home visits. The recording of the mRS at the 90-day follow-up study visit is crucial as it will provide a completely blinded assessment of the primary outcome for MOST. If it is not possible to reach the subject for an in-person interview, the 90-day mRS may be obtained over a recorded telemedicine or video conference. As an absolute last effort to obtain the primary outcome, the 90-day mRS may be obtained over a recorded phone call.

G. STUDYFLOW

Schematic of study treatment administration.



H. SCREENING AND ELIGIBILITY CRITERIA

1. Screening

All patients who present to the participating ED with suspected Acute Ischemic Stroke (AIS) will be identified and screened for potential eligibility in MOST by the stroke team and study coordinator (or other designated member of the study staff). It is well established that time to IV thrombolysis and endovascular thrombectomy when indicated is critical for optimal outcomes, therefore enrollment must occur in parallel with SOC and should not interfere with or delay regular treatment. Patients should be reviewed by appropriate members of the study staff as quickly as possible to determine eligibility for participation and to initiate study procedures. If non-study personnel perform specific assessments that determine eligibility, e.g. NIHSS prior to IV thrombolysis, it is the responsibility of the study team to confirm these items.

Although patients with baseline disability are eligible for MOST, if recrudescence of symptoms from a previous ischemic stroke is suspected the patient should not be enrolled in the trial. Further, in patients with prior neurological deficits, new deficits must total 6 or more points on the NIH stroke scale to be eligible for MOST.

After the decision to treat with IV thrombolysis is made in eligible ischemic stroke patients, the patient or LAR will be approached for participation in the study and informed consent and HIPAA Authorization will be obtained. For patients eligible for Endovascular Thrombectomy (ET), rapid transport to ET should be initiated and facilitated concurrent with discussions regarding the study.

During initial contact with a potential research study candidate and/or LAR, the study staff member should provide a comprehensive explanation of the purpose, procedures, and possible risks/benefits of the study in language that is understandable to a non-medically trained person. Research staff should also explain the participant's responsibilities, the fact that his/her participation is voluntary, that he/she may withdraw from the study at any time, and that the decision not to participate or to withdraw from the study will not affect the subject's medical care in any way. Potential participants or their LARs should be given the opportunity to read the ICD, to ask questions and to consider their decision. If the participant or the LAR confirms interest, a signed and dated written ICD and HIPAA Authorization will be obtained. Informed consent must be obtained by members of the study team who are qualified to perform this task and designated this responsibility on the DOA.

To ensure successful site recruitment performance, it is recommended that the CPS PI discuss the optimal approach to obtaining informed consent and HIPAA Authorization with all of the designated members of the study team at their site emphasizing that consent must be secured prior to any study related activity. Informed consent must always be obtained prior to any study related procedures. Due to the acute nature of this trial, the CIRB has approved an ICD that has been minimized to include only the elements of informed consent required by 21CFR50.25. An information sheet detailing all other supplemental information will be provided to the patient or LAR after informed consent is obtained. The format of both the ICD and MOST Participant Study Information Sheet follow recommendations from the FDA and Clinical Trials Transformation Initiative (CTTI) on this tiered approach to informed consent.

Should a CPS be participating in other trials that are in direct competition with MOST, a planned allocation of enrollment must be put into place in those hospitals actively enrolling patients in multiple studies, thereby preventing preferential enrollment into any one trial.

1.1 Screen Failure Report

AIS patients who receive IV thrombolysis <u>within 3 hours</u> but are deemed ineligible and are not randomized will be entered onto the Screen Failure Report. The screen failure report will be maintained by each CPS documenting reasons that potential patients are not randomized. Screen

failures will be entered into WebDCU™ within 5 days. Patient date of presentation and the primary reason for ineligibility will be captured on the screening report. Please refer to the Data Collection Guidelines for more information on how to complete this form in WebDCU™.

Patients who are consented and not randomized are considered screen failures and the reason for not randomizing should be documented.

Submission of form F102 generates the subject's randomized treatment assignment. Randomization cannot be un-done. Once the randomization form is submitted, this subject is randomized in the trial and must be followed until the End of Study visit or withdrawal of consent.

Patients who are consented and randomized, but do not receive study drug for any reason will be considered 'post-randomization' screen failures. These subjects will have a subject ID and a study book posted in their WebDCU™ record and should be followed for the duration of the 90-day study period.

2. Eligibility Criteria

2.1 Clinical Inclusion Criteria

- Acute ischemic stroke patients
- Treated with 0.9mg/kg IV rt-PA or 0.25mg/kg IV TNK within 3 hours of stroke onset or time last known well
- Age ≥ 18
- NIHSS score ≥ 6 prior to IV thrombolysis
- Able to receive assigned study drug within 60 minutes but no later than 75 minutes of initiation of IV thrombolysis

2.2 Clinical Exclusion Criteria

- Known allergy or hypersensitivity to argatroban or eptifibatide
- Previous stroke in the past 90 days
- Previous intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arterial venous malformation
- Clinical presentation suggested a subarachnoid hemorrhage, even if initial CT scan was normal.
- Any surgery, or a biopsy of parenchymal organ in the past 30 days
- Trauma with internal injuries or ulcerative wounds in the past 30 days
- Severe head trauma in the past 90 days
- Systolic blood pressure persistently >180mmHg post-IV thrombolysis despite antihypertensive intervention
- Diastolic blood pressure persistently >105mmHg post-IV thrombolysis despite antihypertensive intervention
- Serious systemic hemorrhage in the past 30 days
- Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR >1.5
- Positive urine or serum pregnancy test for women of child bearing potential
- Glucose <50 or >400 mg/dl
- Platelets <100,000/mm3
- Hematocrit <25 %
- Elevated pre-thrombolysis PTT above laboratory upper limit of normal
- Creatinine > 4 mg/dl
- Ongoing renal dialysis, regardless of creatinine
- Received Low Molecular Weight heparins (such as Dalteparin, Enoxaparin, Tinzaparin) in full dose within the previous 24 hours
- Abnormal PTT within 48 hours prior to randomization after receiving heparin or a direct thrombin inhibitor (such as bivalirudin, argatroban, dabigatran or lepirudin)

- Received Factor Xa inhibitors (such as Fondaparinaux, apixaban or rivaroxaban) within the past 48 hours
- Received glycoprotein IIb/IIIa inhibitors within the past 14 days
- Pre-existing neurological or psychiatric disease which confounded the neurological or functional evaluations e.g., baseline modified Rankin score >3
- Other serious, advanced, or terminal illness or any other condition that the investigator felt would pose a significant hazard to the patient if rt-PA, TNK, eptifibatide or argatroban therapy was initiated (Example: known cirrhosis or clinically significant hepatic disease)
- Current participation in another research drug treatment or interventional device trial - Subjects could not start another experimental agent until after 90 days
- ICF from the patient or the legally authorized representative was not or could not be obtained
- High density lesion consistent with hemorrhage of any degree
- Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT Scan. Sulcal effacement and/or loss of grey-white differentiation alone are not contraindications for treatment

I. INFORMED CONSENT AND HIPAA AUTHORIZATION

In accordance with FDA regulations (21 CFR 50) and International Council for Harmonization-GCP Consolidated Guidelines, a witnessed, CIRB-approved, informed consent is required from all patients prior to study participation. All qualified MOST 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 ICD and HIPAA Authorization are obtained from each participant or LAR ***before*** the participant participates in any study related activity even when this task has been delegated to other individuals on the study team.

1. Informed Consent and HIPAA Authorization

The ICD 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. 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:

- CPSs are required to use the most **current NIH StrokeNet CIRB approved** ICD and HIPAA Authorization provided to their individual CPS.
    - Confirm use of the most current CIRB approved ICD and HIPAA Authorization ***prior*** to initiating the informed consent process. <u>If you do not have the most current version, know where to get it.</u>
- Informed consent and HIPAA Authorization must be obtained before initiating any study related activity - no exceptions.
- In addition to signing the ICD and HIPAA Authorization, the patient/LAR should enter the date of signature on the consent documents, to permit verification that consent was actually obtained before the participant began participation in the study.
    - Since informed consent will be obtained the same day that the participant's involvement in the study begins, <u>the participant's medical record should document that consent was obtained prior to participation in the research</u>.
- The CIRB has given approval that informed consent and HIPAA Authorization can be obtained from the patient or LAR if patient is deemed decisionally impaired as a result of their enrolling stroke.
    - 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.
    - <u>If no LAR is available and the individual is unable to give consent, the prospective participant should NOT be randomized in the MOST trial</u>.
- The original ICD and HIPAA Authorization should be retained in the study/participant file in a secure/confidential manner.
- A copy of the ICD and HIPAA Authorization must be provided to the participant.
    - FDA regulations do not require the participant's copy to be a signed copy, although a photocopy with signature(s) is preferred.
- A non-redacted ICD and HIPAA Authorization will be uploaded as one document by local site coordinator into WebDCU for remote monitoring by NDMC personnel.
- 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.

1.1 Foreign Language ICD and HIPAA Authorization Documents

Translation of foreign language ICD and HIPAA Authorization will be according to StrokeNet SOP Number: ADM 11.

1.2 Informed Consent and HIPAA Authorization via Telemedicine

Telemedicine procedures may be used for informed consent and HIPAA Authorization per approval by the CIRB.

1.3 Informed Consent and HIPAA Authorization using Remote Procedures

Remote procedures may be used for informed consent and HIPAA Authorization according to StrokeNet SOP Number: GCP 13, or according to local procedures per approval by the CIRB. Electronic consent (eConsent) is a method that falls under the category of remote consent. The StrokeNet NCC manages a central eConsent platform through REDCap that is available for use according to the StrokeNet Central eConsent SOP.

2. HIPAA Authorization

Under U.S. federal law, researchers who use information about the health of their research participants are required, except in specific circumstances, to get written permission to use their participant's protected health information (PHI) for the research study. Each CPS is expected to comply with StrokeNet SOP Number: GCP 05.

3. Participant Study Information Sheet

Each participant or LAR will receive a copy of the Participant Study Information Sheet at the time of the informed consent process.

J. RANDOMIZATION

After confirming eligibility and obtaining informed consent and HIPAA Authorization, the patient will be entered as a subject into the WebDCU™ system, which centrally randomizes and assigns the subject ID number, treatment arm, and calculates the participant's weight-based dosing information. The study team should not randomize in WebDCU™ until IV thrombolysis is actually administered to the patient to ensure all eligibility criteria are met.

When an eligible patient at the CPS is ready to be randomized, an authorized study team member will log onto WebDCU™ in order to data enter and submit the required Subject Enrollment Form and F102 Randomization. Prior to entering this Randomization Form, the informed consent and HIPAA Authorization must be signed and the subject must meet all eligibility requirements on F101 Eligibility. However, due to time constraints, F101 does not need to data entered in WebDCU™ prior to randomization. Upon successful randomization, sites will print, complete and file the MOST Randomization Verification Form for source documentation.

Randomization cannot be un-done. Once the randomization form is submitted, this subject is randomized in the trial and must be followed until the End of Study visit or withdrawal of consent.

Complete step-by-step instructions on how to randomize a subject in WebDCU™ can be accessed at https://webdcu.musc.edu/login.asp, "MOST → Toolbox → Project Documents → MOST Randomization Instructions".

1. Emergency Randomization Instructions

If a problem occurs during the randomization process, please contact the **WebDCU™ Emergency Randomization Hot Line at 1-866-450-2016.** This hotline is only for randomization emergencies and is available 24 hours a day, 7 days a week.

NOTE: Questions regarding eligibility or protocol implementation should be directed to the **MOST Clinical Hotline: 1-833-229-MOST (6678)**.

K. STUDY INTERVENTION

1. Investigational Product

Upon site initiation, each CPS pharmacy will be provided with 3 study drug kits, one for each arm of the trial. When the CPS dispenses a kit, WebDCU™ will automatically send a drug request to replace the dispensed kit. This algorithm will be assessed and perhaps modified at a later date depending upon site enrollment volume. The site PI is ultimately responsible for the accountability of Investigational Product (IP), or study drug, sent to their site. This responsibility may be delegated to a qualified individual at the site, such as the Site Pharmacist. This assignment should be documented on the MOST DOA (see MOP Section C for detailed training and regulatory document requirements). Documentation of receipt, disposition (destroyed or returned), and dispensing of IP must be maintained on the Study Drug Accountability Log, Study Drug Dispensing Log, and in the WebDCU™ study drug accountability module, as applicable. Storage of IP must be compliant with the instructions provided by the NCC Central Pharmacy. IP should only be used in accordance with the protocol and for participants consented in the trial. Detailed site requirements and pharmacy instructions for the trial are provided in the MOST CPS Study Drug Procedures document.

1.1 Study Arms

1. Argatroban: bolus [100μg/kg]
   0-2 hour dose [3μg/kg/min]
   2-12 hour dose [3μg/kg/min]

2. Eptifibatide: bolus [135μg/kg]
   0-2 hour dose [0.75μg/kg/min]
   2-12 hour placebo dose

3. Placebo: bolus
   0-2 hour dose
   2-12 hour dose

Given the single-blind design, IP for MOST will be sent to CPS pharmacies in its commercially available form. The NCC Central Pharmacy will assemble study drug kits that will contain saline placebo, argatroban or eptifibatide sufficient for administration to the maximum dosing weight of 100kg. It is the responsibility of the site pharmacy to reconstitute and label the study drug according to the CPS Study Drug Procedures document to ensure subjects remain blinded.

All randomized participants will be assigned a study drug kit ID (equal to the randomization code) corresponding to a study drug kit that is in inventory at that site. Subjects in all study arms will receive a bolus, 0-2 hour dose, and a 2-12 hour dose. Study drug for all three treatment arms will be administered according to a weight-based dosing protocol. Weight-based doses for each will be determined by the WebDCU™ system.

2. Dosing and Administration

Participant information is entered into WebDCU™ Form 102 Randomization for entry into the trial, including weight. The WebDCU™ system will determine which arm the participant is assigned to, and calculate their weight-based dosing information: volume of the bolus, rate of the 0-2 hour dose, and rate of the 2-12 hour dose. This information is captured on the MOST Randomization Verification Form, examples below, which sites will print for source documentation.

MOST Randomization Verification Form

Subject ID: 1000

Subject weight: 113.4 kg

Treatment Group: Argatroban

Drug Kit ID assigned by WebDCU™: 80234

ID on Kit retrieved from pharmacy: _ _ _ _ _ _

Signature of the person verifying WebDCU™ Drug Kit ID retrieved from the pharmacy. This verification must take place prior to administration: _____

Printed name of the person listed above: _____

Date: _____

The MOST Clinical PI Hot Line is: 1-833-229-MOST (6678)

MOST Dosing Table

A study team member must initial to verify the doses administered to the subject match the doses listed below.

- Bolus dose: Administer 10 mL over 3 minutes. _____(Initials)
- 0-2 hours dose: Administer 18 mL/hr for 2 hours. Total volume to be infused is 36 mL. _____(Initials)
- 2-12 hours dose: At start, administer 18 mL/hr. Titrate per protocol. Discontinue promptly 12 hours after bolus administration. _____ (Initials)

Printed name of person initialing above: _____

Date: _____

File this with the other source documents for this subject.

Form Generated Timestamp: 9/8/2021 3:44:15 PM EST

MOST Randomization Verification Form

Subject ID: 1000

Subject weight: 113.4 kg

Treatment Group: Placebo

Drug Kit ID assigned by WebDCU™: 80234

ID on Kit retrieved from pharmacy: _ _ _ _ _ _

Signature of the person verifying WebDCU™ Drug Kit ID retrieved from the pharmacy. This verification must take place prior to administration: _____

Printed name of the person listed above: _____

Date: _____

The MOST Clinical PI Hot Line is: 1-833-229-MOST (6678)

MOST Dosing Table

A study team member must initial to verify the doses administered to the subject match the doses listed below.

- Bolus dose: Administer 10 mL over 3 minutes. _____(Initials)
- 0-2 hours dose: Administer 18 mL/hr for 2 hours. Total volume to be infused is 36 mL. _____(Initials)
- 2-12 hours dose: At start, administer 18 mL/hr. Titrate per protocol. Discontinue promptly 12 hours after bolus administration. _____ (Initials)

Printed name of person initialing above: _____

Date: _____

File this with the other source documents for this subject.

Form Generated Timestamp: 9/8/2021 3:44:15 PM EST

MOST Randomization Verification Form

Subject ID: 1000

Subject weight: 113.4 kg

Treatment Group: Eptifibatide

Drug Kit ID assigned by WebDCU™: 80234

ID on Kit retrieved from pharmacy: _ _ _ _ _ _

Signature of the person verifying WebDCU™ Drug Kit ID retrieved from the pharmacy. This verification must take place prior to administration: _____

Printed name of the person listed above: _____

Date: _____

The MOST Clinical PI Hot Line is: 1-833-229-MOST (6678)

MOST Dosing Table

A study team member must initial to verify the doses administered to the subject match the doses listed below.

- Bolus dose: Administer 10 mL over 3 minutes. _____(Initials)
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- 2-12 hours dose: At start, administer 18 mL/hr. Titrate per protocol. Discontinue promptly 12 hours after bolus administration. _____ (Initials)

Printed name of person initialing above: _____

Date: _____

File this with the other source documents for this subject.

Form Generated Timestamp: 9/8/2021 3:44:15 PM EST

The CPS pharmacy should generate an order to allow administration of the study drug according to the dosing information provided through WebDCU™. The volume administered for each participant will vary depending on their weight, therefore **there will likely be substantial unused IP left after dosing**. It is likely that IP will be administered while the IV thrombolytic is infusing, therefore a separate IV line that is dedicated to the 12-hour study drug regimen should be established, particularly for patients who receive rt-PA. See Appendix 1 for a list of medications commonly given to AIS patients and their compatibility with MOST study drug when administered through the same IV site.

The rate of the 2-12 hour dose for participants randomized to receive argatroban may be titrated based on the 2 and 6-hour aPTT. See Section K.3, Argatroban Titration Protocol.

2.1 Bolus

A 100ml glass vial for the eptifibatide arm and a 100ml IV bag for the argatroban and placebo arms will contain both the bolus dose and the 0-2 hour dose. The bolus should be withdrawn from the vial/bag by the pharmacy and administered to the subject over a 3-minute IV push or via a pump system. Depending on the treatment arm, the volume of the bolus may be as much as 18mL.

Every effort should be made to administer study drug as soon as possible after thrombolysis, but no later than 75 minutes from thrombolysis bolus administration. Study drug bolus should be administered to eligible, randomized subjects regardless of clinical improvement prior to study drug initiation.

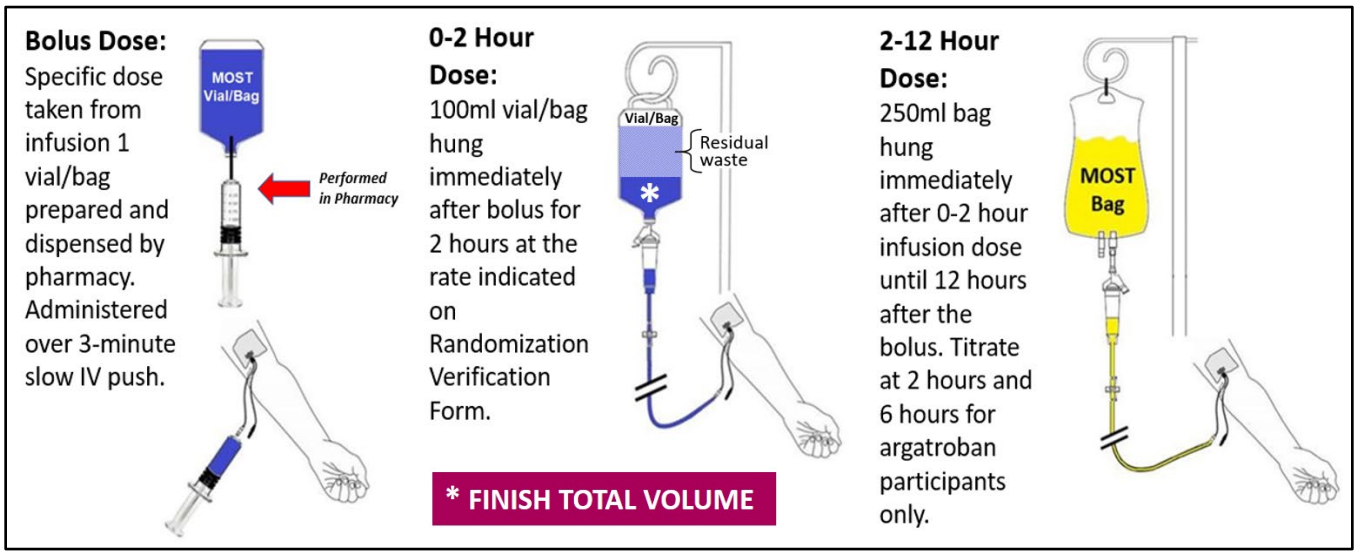
2.2 0-2 Hour Dose

Immediately after administering the bolus dose, the 100ml vial/bag will be hung directly on an IV pole for administration of the 0-2 hour dose through a pump. The pump and tubing set-up should be prepared for the 0-2 hour dose before the bolus is administered to ensure a seamless transition between doses. Infusion of the full volume to be infused (VTBI) for the 0-2 hour dose indicated on the Randomization Verification Form for each participant will take 2 hours. There will be unused IP remaining in the vial/bag after the VTBI is infused. **The vial/bag and all associated tubing should be completely removed when the VTBI is completed.**

2.3 2-12 Hour Dose

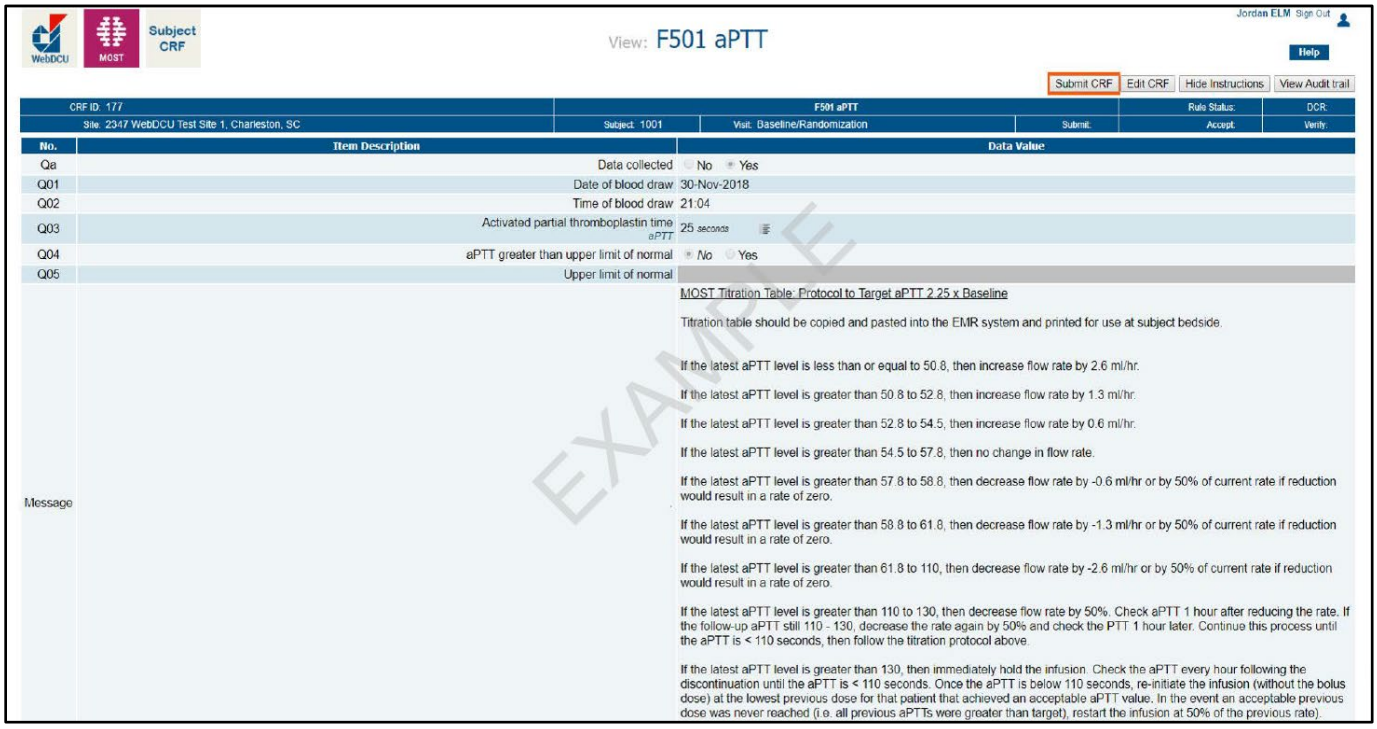
The 250ml bag will contain the 2-12 hour dose. After the end of the 0-2 hour dose, the 2-12 hour dose should be hung immediately using a new primary tubing set-up. **Study personnel are expected to remain on-site until the 2-12 hour dose has been initiated to oversee appropriate dosing.**

The 250ml bag and all associated tubing should be completely removed promptly at 12 hours after initial study drug bolus administration. Study drug termination should occur 12 hours +/- 30 minutes after the time of the bolus dose.



3. Argatroban Titration Protocol

The 2-12 hour dose rate for argatroban arm subjects may be titrated based on the aPTT value collected at 2 hours and at 6 hours after the time of the bolus. Study staff will enter the baseline aPTT value for argatroban subjects into F501 aPTT, which will generate the MOST Titration Table. The subject's 2 and 6-hour aPTT values will be compared to the MOST Titration Table, example below, to determine the appropriate titration. The argatroban dose rate should be titrated as soon as aPTT values are available.



WebDCU | MOST | Subject CRF

View: F501 aPTT

Jordan ELM Sign Out | Help

Submit CRF | Edit CRF | Hide Instructions | View Audit trail

CRF ID: 177		F501 aPTT			Rule Status:	DCR:
Site: 2347 WebDCU Test Site 1, Charleston, SC		Subject: 1001	Visit: Baseline/Randomization	Submit:	Accept:	Verify:

No.	Item Description	Data Value
Qa	Data collected	No / Yes
Q01	Date of blood draw	30-Nov-2018
Q02	Time of blood draw	21:04
Q03	Activated partial thromboplastin time aPTT	25 seconds
Q04	aPTT greater than upper limit of normal	No / Yes
Q05	Upper limit of normal	
Message		MOST Titration Table: Protocol to Target aPTT 2.25 x Baseline Titration table should be copied and pasted into the EMR system and printed for use at subject bedside. If the latest aPTT level is less than or equal to 50.8, then increase flow rate by 2.6 ml/hr. If the latest aPTT level is greater than 50.8 to 52.8, then increase flow rate by 1.3 ml/hr. If the latest aPTT level is greater than 52.8 to 54.5, then increase flow rate by 0.6 ml/hr. If the latest aPTT level is greater than 54.5 to 57.8, then no change in flow rate. If the latest aPTT level is greater than 57.8 to 58.8, then decrease flow rate by -0.6 ml/hr or by 50% of current rate if reduction would result in a rate of zero. If the latest aPTT level is greater than 58.8 to 61.8, then decrease flow rate by -1.3 ml/hr or by 50% of current rate if reduction would result in a rate of zero. If the latest aPTT level is greater than 61.8 to 110, then decrease flow rate by -2.6 ml/hr or by 50% of current rate if reduction would result in a rate of zero. If the latest aPTT level is greater than 110 to 130, then decrease flow rate by 50%. Check aPTT 1 hour after reducing the rate. If the follow-up aPTT still 110 - 130, decrease the rate again by 50% and check the PTT 1 hour later. Continue this process until the aPTT is < 110 seconds, then follow the titration protocol above. If the latest aPTT level is greater than 130, then immediately hold the infusion. Check the aPTT every hour following the discontinuation until the aPTT is < 110 seconds. Once the aPTT is below 110 seconds, re-initiate the infusion (without the bolus dose) at the lowest previous dose for that patient that achieved an acceptable aPTT value. In the event an acceptable previous dose was never reached (i.e. all previous aPTTs were greater than target), restart the infusion at 50% of the previous rate).

EXAMPLE

Collection of the aPTT specimen should occur within the 2-hour (± 30 minutes) window and similarly within the 6-hour (± 30 minutes) window, according to the WebDCU™ generated instructions.

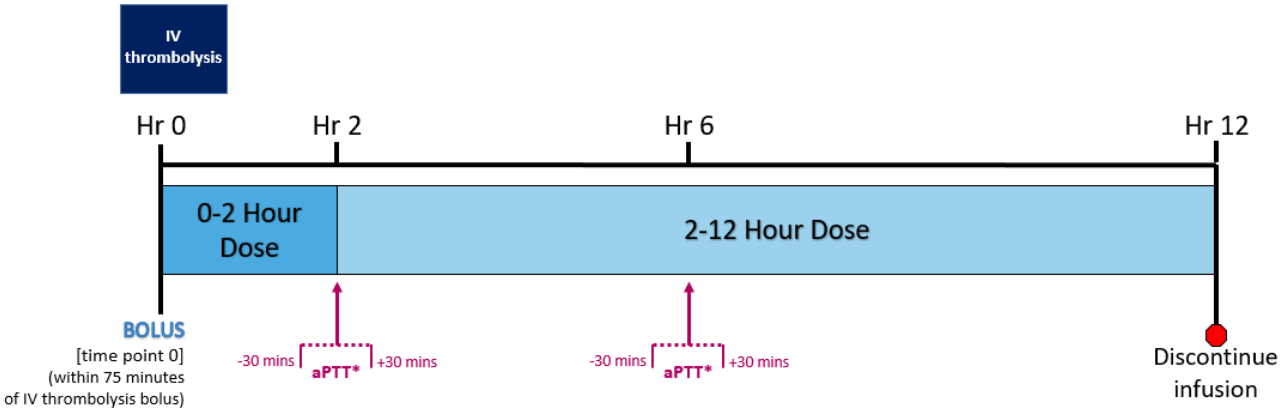
3.1 2 Hours (± 30 Minutes)

Within 2 hours after initial study drug bolus (± 30 minutes), an aPTT lab will be collected via venous draw per local laboratory procedures for argatroban arm subjects. **The aPTT should be collected from the arm that is opposite of the argatroban infusion. Finger stick aPTT collection is prohibited.** The aPTT should be collected as early in the 2-hour (± 30 minutes) window as possible to allow time for the sample to be processed and resulted.

If the 2-hour aPTT value is not available from the lab by the end of the 0-2 hour argatroban dose, the 2-12 hour dose should be administered at the rate that was initially calculated by WebDCU™, which will be the same rate as the 0-2 hour dose. In this case, once the 2-hour aPTT value is available the study team should assess the result and titrate the dose rate of the 2-12 hour dose per the MOST Titration Table. If a scheduled aPTT draw is missed, the specimen should be collected and the study drug dose rate titrated as soon as possible.

3.2 6 Hours (± 30 Minutes)

Another aPTT specimen collection will occur at 6 hours (± 30 minutes) after initial argatroban bolus. Similarly, the aPTT should be collected as early in the 6-hour (± 30 minutes) window as possible to allow time for the sample to be processed and resulted to determine if dose rate titration is indicated based on the MOST Titration Table. If a scheduled aPTT draw is missed, the specimen should be collected and the study drug dose rate titrated as soon as possible.



ARGATROBAN ONLY* 2-12 hour infusion dose titration instructions:

1. Enter the baseline aPTT value in WebDCU™ under **Form 501 aPTT** and print the MOST Titration Table that is generated
2. Collect aPTT specimen as early in 2 and 6 hour windows as possible to allow time for processing and for the value to result
3. Based on the result of the aPTT increase, decrease, or make no change to the rate of the argatroban 2-12 hour infusion dose according to the Titration Table

4. Infusion Interruptions

Interruptions to study drug infusion should be minimized as much as possible to ensure that the intended dose is administered to the subject. If the 0-2 hour dose is interrupted and is then restarted, the remainder of the dose, or volume to be infused (VTBI) should be completed. If the 0-2 hour dose runs over the 2-hour time point, the aPTT in argatroban arm subjects should still be collected at 2 hours (± 30 minutes) from bolus administration.

If the 2-12 dose is interrupted and then restarted, it should still be terminated promptly 12 hours after initial study drug bolus administration regardless of the duration of the interruption(s). If less than the intended dose and duration of study drug is administered to the subject, the reason why study drug was not administered in full should be documented on F206 Study Drug Administration.

In the case that venous access has been lost after initiation of study drug, the study infusion should be restarted as quickly as possible after the clinical team establishes access per standard practice. If venous access is lost before a subject is administered the study drug bolus; venous access must be reestablished, per local standard practices, and study drug bolus given within 75 minutes of initiation of thrombolysis. If a scheduled aPTT draw is missed due to loss of venous access, the specimen should be collected as soon as possible and the study drug titrated accordingly.

5. Documentation of Administration

It is imperative to maintain accurate documentation on F206 Study Drug Administration. It is advised that this case report form should be printed out and be available at the bedside, alongside the MOST Titration Table, for the duration of the infusion to capture the details every time a dose (vial/bag) is changed, a rate is changed, or there is an interruption in the infusion.

There is no need to keep the study drug vials after administration is complete as long as accurate accountability is ensured per F206 Study Drug Administration and CPS institutional policy. For more information on how to complete F206 in WebDCU™ please see the Data Collection Guidelines.

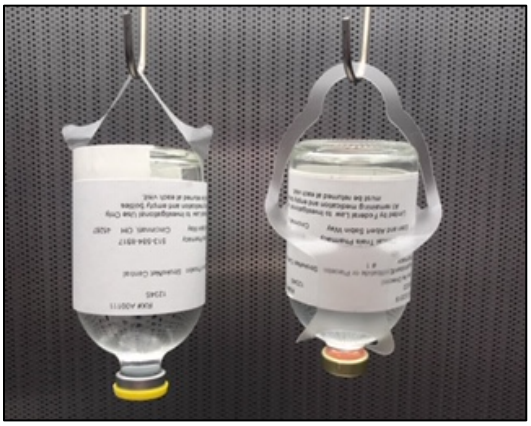
L. BLINDING AND MONITORING FOR BIAS

1. Blinding

Argatroban and placebo subjects will initially receive a bolus followed by a 12-hour dose. Eptifibatide arm subjects will receive a bolus followed by a 2-hour dose. A 10-hour saline infusion will be administered after the 2-hour eptifibatide dose to maintain the single blind. Investigators are unblinded to treatment arms, but subjects and LARs are blinded throughout the duration of the trial. Single blinding is achieved through the use of labels which cover trial drugs or glass vials and normal saline bags (example below).

Eptifibatide 0-2 hour dose (100 mL glass vial)

Front



Back

Argatroban and Placebo 0-2 hour dose (100 mL bag) and 2-12 hour dose for all arms (250 mL bag)

Front

Back

2. Blinded Outcomes Assessments

Although the bedside, clinical treatment team may discover the treatment assignment, every effort will be undertaken so additional members of the stroke team and/or the research team remain unaware of the treatment assignment. The 24-hour NIHSS must be performed by a blinded assessor. The 30-day and 90-day mRS should also be performed by a blinded assessor.

3. Monitoring for Bias

Blinded aggregate information on demographic characteristics of MOST participants will be reviewed after each 100 enrollments in an effort to ensure representative enrollment of minorities. If an inadequate representation of minorities is detected, the study team will consider refocusing recruitment efforts towards sites with larger proportions of minorities as warranted.

M. PARTICIPANT EVALUATIONS AND FOLLOW-UP

Schedule of Events							
Time	**Baseline**	**2 hour (+/- 30 min) (after start of study drug)**	**6 hour (+/- 30 min)**	**24 hours (+/- 12 hrs)**	**Day 3/Discharge* (+/- 24hrs)**	**Day 30 (+/- 7 days)**	**Day 90 (+/- 14 days)**
Inclusion Exclusion Criteria	X						
Subject Enrollment	X						
Informed Consent/ Randomization	X						
History & Physical[#]	X						
NIH Stroke Scale	X			X			
Modified Rankin Score	X					X	X
Consent Experience Survey					X		
EQ-5D							X
CT/MRI scan (SOC[#])	X			X			
CTA/MRA (if SOC)	X						
CBC with platelets[#]	X						
Glucose, electrolytes, BUN/creatinine, PT[#]	X						
aPTT[#]	X	X	X				
Dosing Titration[$]∞		X	X				
Adverse Events	X	X	X	X	X	X^	X^
End of Study							X

[#]Standard of care *whichever comes first ^serious AEs only [$]argatroban arm only ∞as needed based on aPTT titration protocol

1. Baseline

- Inclusion and Exclusion Assessment
- Informed Consent and Randomization
- History and physical
- NIH Stroke Scale (obtained prior to initiation of IV thrombolysis)
- Modified Rankin Score (indicating status prior to qualifying AIS)
- aPTT lab draw
- Labs
- Computed Tomography Angiography (CTA)/Magnetic Resonance Angiography (MRA) and non-contrast CT or MRI (Standard of Care)
- Bolus dose
- Initiation of 0-2 hour dose
- Adverse Event assessment

Any procedures or evaluations that determine inclusion/exclusion in the trial, but are not part of standard care (for example; aPTT test results) must be obtained after the MOST ICD is signed and dated by the participant or LAR. Study personnel must ensure that informed consent and HIPAA Authorization are obtained and inclusion and exclusion criteria are met before a patient is randomized into the trial.

2. 2 Hours (± 30 minutes) after start of study drug

- aPTT lab draw (argatroban arm only)
- Administration of 2-12 hour dose
- Titration of 2-12 hour dose based upon aPTT value (if indicated for argatroban arm only)
- Adverse Event assessment

3. **6 Hours (± 30 minutes) after start of study drug**

- aPTT lab draw (argatroban arm only)
- Titration of 2-12 hour dose based upon aPTT value (if indicated for argatroban arm only)
- Adverse Event assessment

4. **24 Hours (± 12 hours) after start of study drug**

- NIH Stroke Scale (assessor should be blinded to treatment assignment)
- Repeat non-contrast CT or MRI scan (Standard of Care)
- Adverse event assessment

5. **Day 3/Discharge (± 24 hours) whichever comes first**

- Adverse Event assessment
- Consent Experience Survey (up to Day 30)

6. **Day 30 (± 7 days)**

- Rankin Focused Assessment structured interview (in-person or over the phone, assessor should be blinded to treatment assignment)
- Serious Adverse Event assessment only

7. **Day 90 (± 14 days)**

- Rankin Focused Assessment structured interview (in-person and video recorded, assessor should be blinded to treatment assignment)
- EQ-5D-5L
- Serious Adverse Event assessment only

8. **End of Study**

The end of study (EOS) visit can potentially occur at different time points depending upon the subject's disposition. If the participant completes the trial in its entirety, 126 End of Study should be completed after the 90-day follow-up visit is completed. If the subject expires or withdraws from the trial for any reason prior to the 90-day visit, F126 End of Study should be completed upon investigator notification of such event.

9. **Consent Experience Survey**

Between 24 hours and hospital discharge, a brief survey of the consent experience should be obtained from the subject or surrogate who signed the ICD. If the survey cannot be administered before discharge, it can be collected up to the Day 30 visit. If the survey is administered after hospital discharge, it can be collected by sending a paper copy in a pre-stamped envelope or emailing a scanned copy to the person who signed the ICD. While it is preferable to have the person who signed the ICD (subject or surrogate) fill out the survey themselves, the survey can be administered over the phone if this is done by someone other than the team member who conducted the initial consent process.

Every effort should be made to collect the survey and enter it into WebDCU™ under Study Progress – Consent Survey. However, if it cannot be obtained it will not result in a protocol deviation.

10. **90-day mRS**

The protocol requires the 90-day mRS assessment for all MOST subjects to be video recorded for centralized blinded adjudication. Due to the single-blind design, the primary outcome is highly dependent upon centralized blinded review. Local personnel performing the 90-day mRS should be blinded to study treatment and should utilize the Rankin Focused Assessment structured interview.

The centralized blinded adjudication will be performed at the University of Glasgow. The Glasgow team, in conjunction with the CCC, will supply each site with a video camera upon site initiation. One camera will be provided to each site to use for the duration of the trial. The sites should ensure that the

cameras are handled with care as to not be misplaced or damaged. If a CPS does not meet enrollment requirements or is discontinued as a participating site for any reason, the CCC will request that the camera be returned.

Each site will be required to register an account at http://www.glasgowctu.org/mRSPortal/login.asp in order to login and upload the video recordings.

Refer to the **Guidance for Performing and Recording the modified Rankin Scale Assessments** document for detailed instructions located in WebDCU™ under “ToolBox”→”Project Documents”.

N. Participant Retention

1. Missing Data/Lost to Follow-up (LTFU)

All effort is put forth to ensure complete follow-up for all randomized MOST participants, in particular with the assessment of the primary outcome (mRS at 90 days).

Study staff should maintain consistent contact with participants in order to obtain study information, schedule follow-up visits and minimize LTFU. At the time of enrollment, study staff should verify the participant's contact information and collect contact information for as many family members and/or other close relatives as possible. When scheduling follow-up visits, multiple attempts should be made in order 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 in order 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 determine the participants' 90-day mRS status. A participant may be considered LTFU if he or she cannot be reached for up to 150 days from randomization, despite following the procedures outlined above. The following are considered to be reasons a subject is LTFU: unable to contact for follow-up, opted to withdraw from the trial, moved away from and unable to return for follow-up visits, or became ill and unable to communicate. Appropriate documentation of LTFU will be maintained in the subject's research record at the CPS. For subjects considered lost to follow-up, the Social Security Death Index should be referenced to attempt to ascertain the subject's status.

2. Withdrawal of Consent

Every 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 the institution. Written documentation of the participant's decision to withdraw consent should be retained in the participant file in a secure/confidential manner. The participant data collected prior to the time of withdrawal will remain as part of the study records.

O. Concomitant Treatments

1. Discouraged Concomitant Medications

Participants enrolled in MOST will be treated with the standard of care thrombolytic, potentially in combination with argatroban or eptifibatide. Therefore, it is critical that study teams implement a systematic approach to managing these participants to avoid the use of additional antithrombotic, or blood thinning, medications for the first 24 hours after initiation of IV thrombolysis per SOC recommendations.

If a scenario requires any class of antithrombotic medication within 24 hours from IV thrombolysis, the clinical team must have strong justification and a head CT for safety assessment must be performed prior to administration. The route, frequency, dose and duration of the antithrombotic medication should be documented in the general comments section of F173 Thrombolysis Administration. If an antithrombotic is administered within 24 hours from IV thrombolysis and no head CT is performed prior to administration, an Unanticipated Event Report will be reported and will include the route, frequency, dose and duration of the antithrombotic medication.

After 24 hours from IV thrombolysis, antithrombotic medications may be started per usual care.

The following list gives examples of common antithrombotic medications:

Antiplatelets Taken by mouth		**Anticoagulants Taken by mouth**		**Thrombolytics Given through vein ("IV")**	
Aspirin/dipyridamole (Aggrenox)	Prasugrel (Effient)	Warfarin (Coumadin)	Edoxaban (Savaysa)	Alteplase (Activase)	Reteplase (Retavase)
Aspirin	Ticagralor (Brilinta)	Dabigratran (Pradaxa)	Rivaroxaban (Xarelto)	Defibrotide (Defitelio)	Tenectaplase (TNKase)
Cilostazol (Pletal)	Ticlopidine	Apixaban (Eliquis)	Betrixaban (Bevyxxa)		
Clopidogrel (Plavix)	Vorapaxar (Zontivity)				
Dipyridamole		**Anticoagulants Given through vein ("IV") or skin ("SQ")**		**Heparin and Heparin derivatives Given through vein ("IV") or skin ("SQ")**	
Antiplatelets Given through vein ("IV")		Argatroban-IV	Fondaparinux (Arixtra)-SQ	Heparin-IV or SQ	Dalteparin (Fragmin)-SQ
Abciximab (ReoPro)	Tirofiban (Aggrastat)	Bivalirudin (Angiomax)-IV	Lepirudin-SQ	Enoxaparin (Lovenox)-SQ	Tinzaparin (Innohep)-SQ
Eptifibatide (Integrilin)		Desirudin (Iprivask)-IV			

2. Endovascular Therapy

Endovascular therapy (ET) should be offered to all clinically eligible patients as part of standard of care. ET should be performed within current guidelines using approved devices. The clinical treatment process occurs independent of the study, IV thrombolysis then on to ET if indicated. Study drug bolus and infusions will need to be coordinated with ET. The bolus could occur in the angio suite for some subjects. Patients with bolus prior to angio will come up with an additional (if rt-PA is still dripping) infusion of study drug.

Owing to safety concerns related to the administration of additional antithrombotics, performance of procedures or administration of additional antithrombotics outside of the standard of care should be avoided. These are outlined below:

1. Additional IV or IA antithrombotics or thrombolytics during the procedure, other than heparinized saline flush, are protocol violations.
2. Intracranial stenting is a protocol violation.
3. Stenting of proximal carotid stenosis or occlusion should be avoided, if possible. We encourage angioplasty alone. For example, if there is an adequate channel after angioplasty, with good flow, treatment of that stenosis should be delayed at least 24 hours.
4. If an intraprocedural stent is absolutely necessary, the following are reasonable approaches for oral antiplatelets that balance the risk and benefit for patients with acute carotid stents. These regimens are our suggestions based on varied current practice across many institutions. We are not requiring a particular protocol.
    a. No oral antiplatelets until 24 hours after IV thrombolysis and a follow up head CT or MR. ***OR***
    b. Start 325 ASA per NG or PR at: end of the procedure (placebo arm); end of the eptifibatide dose or EVT procedure (whichever is later); or at the end of the argatroban dose at 12 hours. A second oral antiplatelet can be started at 24 hours after a CT or MR that defines size of infarction or hemorrhage. ***OR***
    c. Similar ASA approach as B, but starting the second oral antiplatelet sooner (within 24 hours). In these cases, we recommend getting a CT or MR before starting the second agent to exclude hemorrhage. N.B. Hemorrhage may be difficult to exclude in some cases, owing to contrast staining.

The bolus and full dose of the study medications should be administered to all randomized patients regardless of:

1. Angiographically recanalized between CTA and the initial angiogram (no ET)
2. Completely recanalized post ET – unlikely that this would occur prior to bolus administration, but possible with a 75 minute window from IV thrombolytic bolus to study drug

The treatment team making the decision for ET will be blinded to treatment assignment until the ET procedure is started. Once started, the ET team can ask for treatment assignment information if there are safety concerns related to the procedure and study drugs.

P. SAFETY REPORTING

The following information is intended to provide event reporting guidance for investigators participating in the MOST trial inclusive of adverse events, serious adverse events, and unanticipated or unexpected problems involving risks to participants or others. The guidelines outlined herein incorporate common data elements and are in compliance with both the FDA and Health and Human Services (HHS) defined Code of Federal Regulations (CFR) for the protection of human research participants, the procedures and requirements governing the use of Investigational New Drug (IND), and the monitoring of serious and unexpected adverse events codified under Title 21 CFR part 56 (Institutional Review Boards), part 312 (Investigational New Drug) and 45 CFR part 46 (Protection of Human Participants).

The objectives of this section are to:

- Outline expanded policies and procedures described in the MOST protocol for monitoring the safety of participating research participants for the FDA, DSMB, NIH/NINDS, and CIRB;
- Ensure that the review and reporting of serious adverse events and unexpected/unanticipated problems occur in a timely, meaningful way so that participants can be better protected from avoidable harms.

1. Reportable Event Definitions

1.1 Adverse Event (AE)

An AE is defined as any untoward event or complication that was not previously identified, or that occurs with greater frequency or severity than previously reported, which occurs during the protocol intervention or during the follow-up period, whether or not considered related to the protocol intervention.

For the MOST trial, non-serious adverse events will be reported from the time of randomization through Day 3 or discharge, whichever is earlier.

1.2 Serious Adverse Event (SAE)

AEs are classified as either serious or non-serious. An SAE is any adverse event that results in any of the following outcomes or actions:

- Death due to any cause;
- A life-threatening adverse experience (i.e., the subject was at immediate risk of death from the event as it occurred);
- Inpatient hospitalization or prolongation of existing hospitalization. (Hospitalizations scheduled before enrollment for an elective procedure or treatment of a pre-existing condition that has not worsened during participation in the study is not considered a serious adverse event);
- A persistent or significant disability/incapacity (i.e., a substantial disruption of one's ability to conduct normal life functions);
- A congenital anomaly/birth defect; and,
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (e.g., a new diagnosis of cancer made after study enrollment is considered an important medical event)

An adverse event that does not meet any of the criteria for seriousness listed above should be regarded as a non-serious AE.

All SAEs will be recorded from the time of randomization through the end of the study period.

1.3 Anticipated AEs

The definition of an anticipated adverse event is an adverse event that can be related to the study drug intervention and is identified in the protocol, informed consent or safety monitoring plan as having been

observed with the drug(s) under investigation. For MOST, examples of anticipated, or study drug related, adverse events include:

Bleeding:
- Intracranial hemorrhage
- Hematemesis
- Hematochezia
- Bleeding at the site of arterial or venous punctures
- Easy bruising

Allergic reactions:
- Airway reactions
- General reactions
- Skin reactions

Other:
- Stomach discomfort, nausea, diarrhea
- Chest discomfort or shortness of breath
- Unusual heartbeats
- Fever or headache

Certain adverse events can be anticipated to occur in the study population independent of study drug exposure due to consequences of the underlying disease process, i.e. they are known consequences of the disease being treated. These kinds of anticipated adverse events unrelated to study drug should only be reported if they are considered to be serious.

1.4 Unanticipated or Unexpected Events

Unanticipated events include 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 subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, *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.

An unanticipated event is by definition unexpected, whereas an adverse event may be expected or unexpected. Adverse events relate to harm to participants; unanticipated events may involve an increased risk of harm even if no actual harm occurred.

Certain events require prompt reporting by site principal investigators (PI). These are submitted via the WebDCU™ “StrokeNet UAE-PD Report”.

Examples:

A. Internal adverse events that are unexpected, related to the research, and involve new or increased risks to participants or others (*2.7.1);
B. Unanticipated adverse device effects (*2.7.2);
C. Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur (*2.7.3);
D. Events requiring prompt reporting according to the protocol Sponsor (*2.7.4);
E. Complaints made by research participants indicating an unanticipated event, or complaints that cannot be resolved by the research staff (*2.7.5);
F. Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant (*2.7.6);

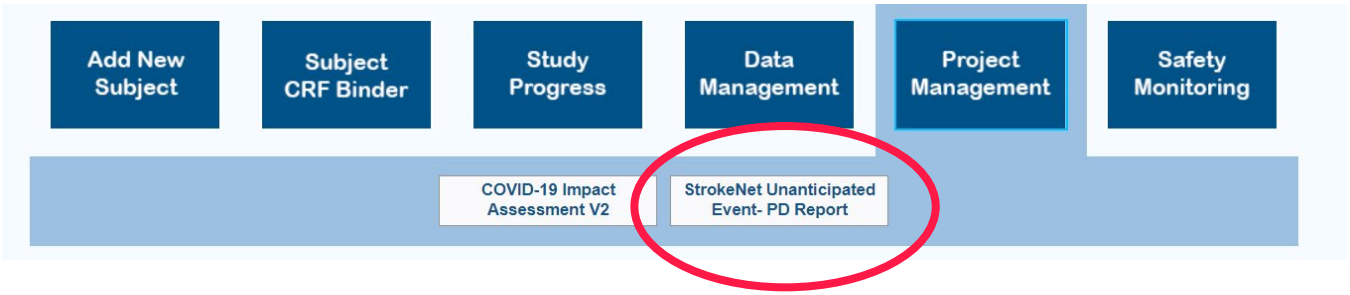
G. Problems or findings (e.g., breach of confidentiality, loss of study data or forms, etc.) that could influence the safe conduct of the research (*2.7.10).

H. Report any new information from written reports (i.e. study monitors, DSMB, etc.) (requirement from UAE-PD form)

** Based on Guidance for The NIH StrokeNet cIRB Event Reporting (HRP-092 SOP: Reporting Unanticipated Problems Involving Risks to Participants and Others, Adverse Events and Other Problems to the IRB)*

For these promptly reportable events, complete "Unanticipated Event Report" (UER) located in WebDCU™ under "Project Management" → "StrokeNet Unanticipated Event-PD Report" and **contact NCC Project Manager for assistance if uncertainty exists surrounding need for event reporting**. The UER will be submitted to the CIRB by the NCC Project Manager on behalf of the site and will provide the site with CIRB letter of acknowledgement following CIRB review.

Events not requiring prompt reporting will be reviewed by the trial study team. The Prime Protocol PI or delegate is responsible for monitoring these in an ongoing manner for events that individually, or in aggregate, should be reported to the CIRB. Events reviewed in aggregate that have the potential to increase the trial's safety risk or threaten data integrity will be submitted to the CIRB, as needed, by the NCC Project Manager on behalf of the Protocol PI or delegate.



2. Adverse Event Reporting

The following attributes will be assigned by the reporting investigator on the eCRF:

1. Description / name of adverse event
2. Grade / Severity
3. Seriousness
4. Relatedness to the study drug(s)
5. Date of onset
6. Outcome
7. Date of resolution (if applicable)
8. Actions taken with study intervention

For more information on how to fill out the AE form, please see the Data Collection Guidelines.

2.1 Description / name of adverse event

To improve the quality and precision of acquired AE data, investigators and coordinators should use correct medical terminology/concepts when reporting AEs or SAEs. Do not use colloquialisms and abbreviations.

- *Diagnosis versus Signs and Symptoms*
  If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record pneumonia rather than fever or productive cough; record urinary tract infection rather than urgency, frequency, dysuria, or hematuria). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available as separate AEs.
- *Death*

When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death". All deaths that occur during the protocol-specified reporting period of 90 days regardless of attribution, will be reported as SAEs.

- *Pre-existing Medical Conditions*
  A pre-existing medical condition is one that is present at the start of the study.
  A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study.
  When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").
- *Hospitalizations for Medical or Surgical Procedures*
  Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo a coronary stenting procedure, record the coronary vascular condition that necessitated the stenting as the SAE.

2.2 Grade / Severity

The severity of adverse events will be documented using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE), as it best fits the diagnostic terminology used in naming the event at the site clinical level (see https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

The severity of Adverse Events should be assessed according to the following CTCAE grading index scale:

- ***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.*
- ***Grade 3: Severe**; medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living.*
- **Grade 4: Life-threatening consequences**; urgent intervention indicated
- **Grade 5: Death** related to AE

2.3 Seriousness

Serious AEs are defined by the FDA and OHRP/HHS and therefore seriousness (not grade / severity) serves as a guide for defining regulatory reporting obligations for patient/subject safety. "Serious" is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning (i.e., death, life-threatening, hospitalization or prolongation of hospitalization, etc. – see Section 1.2).

2.4 Relatedness / Assessment of Causality

Adverse events may be caused by one or more of the following:

- The procedures involved in the trial;
- An underlying disease, disorder, or condition of the subject; or,
- Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject

The investigator, on the basis of his or her clinical judgment and the following definitions, determines the relationship of the AE to the protocol intervention as one of the following:

- Unrelated
  - The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment).

- Unlikely (must have 2 of the following)
  - May have reasonable or only tenuous temporal relationship to intervention.
  - Could readily have been produced by the subject's clinical state, or environmental or other interventions.
  - Does not follow known pattern of response to intervention.
  - Does not reappear or worsen with reintroduction of intervention.
- Reasonable possibility (must have 2 of the following)
  - Has a reasonable temporal relationship to the intervention.
  - Could not readily have been produced by the subject's clinical state or environmental or other interventions.
  - Follows a known pattern of response to intervention.
- Definitely (must have all 4 of the following)
  - Has a reasonable temporal relationship to intervention.
  - 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 intervention.
  - Disappears with reduction on dose or cessation of intervention and recurs with re-exposure.

2.5 Outcome

The site is responsible for active follow-up on all unresolved AEs/SAEs at each subject contact until resolution or end of study (i.e., includes death), whichever occurs first.

2.6 Description of event or problem (required for SAE reporting)

- This section allows space for the site investigator to provide a descriptive narrative of relevant details and events leading up to the SAE being reported. The narrative should be devoid of subject, site, and investigator identity and should be inclusive of the following:
  - Subject age, gender, pertinent history, time & date of symptom onset and study randomization;
  - Dates/times surrounding event and relevant clinical assessments, procedures;
  - Description of what happened, medical/neurologic status prior to event, relevant signs, symptoms;
  - Differential diagnosis for event in question; and,
  - Complete information on clinical course, treatments, and outcomes
- Relevant tests entered should contain the results of the test (e.g., entering that a subject had a head CT along with the summary of results of the scan)
- Other relevant history at a minimum should contain all known pre-existing medical conditions (e.g., hypertension, coronary artery disease, prior stroke)

3. Reporting Requirements

A patient will be considered an enrolled participant at the time of randomization. All events related to participant safety will be assessed starting at the time of randomization through the 90-day follow-up or EOS, whichever is earlier. Each clinical site PI (or designated sub-I) is responsible for active review of all adverse events, serious adverse events, and unanticipated problems ensuring complete data submission into WebDCU™, and submission of follow-up data and query resolution in a timely manner.

3.1 Adverse Events

- All non-serious adverse events observed by the investigator or reported by the participant, will be recorded from the time of randomization through Day 3 or discharge, whichever is earlier.
- Non-serious adverse events will be reported in WebDCU™ within 5 days of the site's awareness of the event.
- Non-serious adverse events will be reported to the CIRB at the time of annual CR.

3.2 Serious Adverse Events

- All SAEs will be recorded from the time of randomization through Day 90.
- All SAEs must be reported in WebDCU™ within 24 hours of site awareness of the event and must be followed for the duration of the study follow-up or until resolution, whichever comes first.
- Death due to the natural history of ischemic stroke will be recorded as a non-related SAE. Additionally, all serious but known complications of stroke (i.e., malignant brain edema) will be recorded as non-related SAEs.
- All SAEs including deaths will be reported to the IMSM, the ESM, the CIRB, and the FDA, as required.
- A written description of the event, relevant tests/laboratory data, relevant medical history and concomitant medications will be required for SAEs and safety outcomes. Safety outcomes include intracranial hemorrhage (asymptomatic and symptomatic) and major hemorrhage (other than intracranial hemorrhage). Major hemorrhage is defined as requiring >2 units of packed red blood cells.
- If an SAE is classified as 'Grade 5' or the type of event is a safety outcome, as described above, an Event Packet is required to be uploaded to WebDCU™. The *MOST Checklist for Preparing Safety Events*, found under "Toolbox → Project Documents", should be used as the SAE Event Packet face page. The CPS should redact all source documents in the SAE Event Packet before submission. The PM will access the event information via the password protected WebDCU™, reviewing the SAE for completeness, deidentification and clinical accuracy. The PM will contact the reporting site requesting additional source documentation surrounding the reported event if inadequate information is available before IMSM review.
  - Form 104 Adverse Event Q22 → click "Edit CRF" → Secure File Upload: Choose File Button → Upload File → Save
- Site submission of an AE eCRF indicating an SAE or ICH will trigger an automatic email from the WebDCU™ system to the NCC Project Manager. Once the PM determines that the SAE has been properly entered and is ready for clinical review, this will be indicated in WebDCU™, which will prompt an automated email to be sent to the IMSM who will access and review the event information, subsequently determining if the AE is serious, unexpected, and related.
- If the IMSM determines the AE to be serious, unexpected and study drug related, a MedWatch report pre-populated with subject data will be generated in WebDCU™.
- Safety reports will be filed with the FDA and CIRB within the required timelines:
  - The sponsor will report unexpected fatal or life-threatening SAEs that are associated with the investigational drug no later than 7 calendar days after the sponsor's initial receipt of information.
  - The sponsor will report unexpected SAEs associated with investigational drug that are not life-threatening no later than 15 calendar days after the sponsor's initial receipt of information.
  - Unexpected SAEs will be reported to the CIRB within 10 days of site awareness of the event.
  - SAEs that are not unexpected will be reported to the CIRB at the time of annual CR.

3.3 Unanticipated Events

- Unanticipated events will be recorded from study start until study close-out.
- Unanticipated events requiring prompt reporting will be reported by the site via the "StrokeNet Unanticipated Event-PD Report" form which is located under the "Project Management Tab" in WebDCU™ (see Section 1.4) within 10 days of site awareness of the event.
- Following form completion/submission, an email notification is automatically sent out to the NCC Project Manager for reporting of the event to the CIRB on behalf of the participating site.

The IMSM will review all ICH cases throughout the trial and will be responsible for ongoing monitoring of reports of SAEs submitted by the clinical centers in real time to ensure GCP and to identify safety

concerns quickly. The IMSM may suggest protocol modifications to prevent the occurrence of particular AEs. In the event of unexpected SAEs or an unduly high rate of SAEs, the IMSM will promptly contact the LPI and the NINDS Program Official who will notify the DSMB Chair.

Q. DATA AND SAFETY MONITORING RESPONSIBILITIES

Safety oversight for this study will be provided by the DSMB, the CIRB, an ESM and an IMSM. Details are provided in the Safety Monitoring Plan.

R. PROTOCOL DEVIATIONS, VIOLATIONS AND REPORTABLE EVENTS

A protocol deviation is defined as an event where the clinical Investigator or site personnel deviate from the study protocol or study procedures. A protocol deviation may be classified as a protocol violation if a subject's rights, safety or well-being are affected, and/or the completeness, accuracy or integrity of study data is compromised. Events classified as protocol violations must be submitted through WebDCU™ as an UER within 10 days of site awareness of the event and subsequently reported promptly to the CIRB. Protocol deviations, or events that do not increase risk to subjects or data integrity, will not require reporting through WebDCU™.

See MOP Section P 1.4 for complete UER reporting requirements.

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

1. Event Reporting Guidance

Certain events require prompt reporting by site principal investigators (PI) such as those that involve increase risk to participants or others. These are submitted via the WebDCU™ "StrokeNet UAE-PD Report". Site PIs do not need to report certain events that are neither serious, nor increase risk to participants or others. These events will be monitored in aggregate by the Protocol PI and the central team to determine if the rate or frequency of events rises to a level of concern that will be reported as a study-level Unanticipated Event Report.

The following is a list of common protocol deviation/violation events and the guidance for reporting each. Please always contact the NCC Project Manager for event reporting clarification.

Event description	Reporting guidance
Incorrect rate, volume or concentration of study drug administered leading to inappropriate dosing.	UER submission required. Event type: Researcher error: failure to follow the protocol due to the action or inaction of the investigator or research staff.
Administration of study drug bolus after 75 minutes from IV thrombolysis.	No UER submission required. Events monitored in aggregate.
Study drug not given or infusion interrupted for any reason.	No UER submission required. Events monitored in aggregate.
2-12 hour study drug infusion terminated after the 12 hour time point.	No UER submission required. Events monitored in aggregate.
aPTT collected outside of 2-hour or 6-hour (± 30 minutes) window.	No UER submission required. Events monitored in aggregate.
24-hour NIHSS, 30 day mRS or 90-day mRS conducted outside of protocol defined window.	No UER submission required. Events monitored in aggregate.
24-hour NIHSS, 30 day mRS or 90-day mRS assessed by an unblinded team member.	No UER submission required. Events monitored in aggregate.
90-day mRS assessment performed but no recording obtained.	No UER submission required. Events monitored in aggregate.
Outdated ICD used.	UER submission required. Event type: 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.

2. Corrective Action Plans

Serious or repeated protocol violations will require the development of a Corrective and Preventive Action (CAPA) plan. Protocol violations that pertain to randomization, enrollment/eligibility and treatment/adherence will be reported to the DSMB. Development of a CAPA plan may be initiated by the site study team, CIRB, the NDMC, or the NCC. Potential triggers include improper consenting practices, protocol deviations, data quality problems, or systematic problems identified by study teams or monitors. A CAPA plan includes a corrective and preventive component. The corrective action describes what action will be taken to correct the deficiency (e.g., re-consenting a subject who was consented with an incorrect form, reporting recurrent protocol deviations to the CIRB). The preventive action describes what will be done to prevent the problem from recurring, or, in the case of identified potential problems, how to prevent the problem from occurring. CAPA plans should address the root cause of the problem with the goal of eliminating the root cause to prevent the problem from occurring again.

Short-term solutions are not preventive actions. Initiation of a CAPA plan will require that appropriate data is captured to ensure progress and elimination of the underlying problem. The type of data to be collected will vary depending on the identified deficiency. CAPA plans must be reviewed and approved by the site study team, CIRB, NCC, CCC and/or NDMC. Once a CAPA plan has been approved and enacted, data must be collected as agreed upon in the plan until the study team demonstrates that the issue has been resolved. The criteria for determining this point will vary depending upon the frequency and severity of the issue.

S. DATA COLLECTION GUIDELINES AND STUDY FORMS

The MOST Data Collection Guidelines can be accessed from the WebDCU™ (https://webdcu.musc.edu/login.asp) via the MOST project icon under “Toolbox” → ”Project Documents” → “MOST Data Collection Guidelines”. The MOST CRF forms are located in WebDCU under “Project Setup” → “CRF Collection Schedule”. All of the CRFs required for a visit are located under the visit name through clicking on the PDF icon.

T. DATA MANAGEMENT

The data management team at the NDMC is involved in a wide scope of tasks to ensure timely and accurate collection and processing of data. Prior to the study initiation, the data management team digitizes the study protocol, develops the case report forms, conducts database end user validation, and provides user training. 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.

U. QUALITY ASSURANCE AND QUALITY CONTROL PROCEDURES

Data quality assurance processes at the NDMC include:

1) Logic and rule checks built into the database;
2) Real-time review of CRF data by DMs;
3) Central monitoring via statistical programming at the NDMC; and
4) Remote and on-site risk-based source verification monitoring by the Clinical Research Associates (CRAs) and DMs at NDMC.

V. SITE MONITORING

The purpose of site data monitoring is to ensure that:

- The rights and well-being of human subjects 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

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 MOST, signed informed consent forms will be uploaded into WebDCU™ and remotely verified by authorized NDMC study team members.

Central monitoring: Data Coordination Unit (DCU) staff members will conduct central monitoring using web-based data validation rules, DM review of entered data, statistical analysis, and on-going review of site metrics.

2. Nature and Extent of On-site Data Monitoring

NDMC, in conjunction with the study team, is responsible for determining the number of anticipated SMVs, based on the complexity of the study design, its phase of development, previous site experience and compliance with study requirements, rate of subject 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 SMVs, routine, for-cause, and closeout visits based upon risks, as well as determining if the site visit may be conducted remotely. Remote SVMs are conducted in the same fashion as on-site visits, except that certain activities may be omitted, such as investigational product accountability. The NDMC relies heavily on central monitoring activities to determine when a SMV is required and to target the work to be performed on-site, in order of priority. The DCU typically skews SMVs 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 SMV will be defined and prioritized by DCU prior to the monitoring visit. All work performed, issues identified, and action items by the monitor will be captured via the WebDCU™ monitoring module. It is expected that each study site will be visited after a small number of subjects are enrolled. At the completion of a site visit, the Monitoring Report will be available for review and sign-off by the site PI via WebDCU™.

W. STUDY COMPLETION AND CLOSEOUT PROCEDURES

At the completion of the trial study staff will need to review the Regulatory and Clinical Data Maintenance and Data Storage SOP Numbers: ADM 21, and GCP 12. These documents will guide the site regarding the expectations for necessary documentation and retention requirements of trial related information. Access to cited NIH StrokeNet Administrative SOPs can be obtained via the following link: http://www.nihstrokenet.org/documents. These documents are in harmony with the Protocol Trial expectations and the StrokeNet Administrative (ADM) and GCP Policies. In addition to these noted SOPs, the CPS may also be required to follow specific local requirements.

A Site Closeout Visit concludes the study at an individual site. 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. The monitor may conduct the visit on-site or remotely, as determined by the NDMC based on the number of subject enrollments, amount and nature of outstanding items to be monitored, and whether the monitor's direct access to the subjects' electronic medical record has been permitted by the institution.

During a Site Closeout Visit, the monitor should complete the items required for a routine monitoring visit. In addition, the monitor should ensure that the items listed in the "Site Requirements" and "Site Monitor Requirements" sections of the site Close-out Checklist are complete. Once the required sections are complete, the Close-Out Checklist will be uploaded into WebDCU™.

X. POLICIES

1. Publications Policy

Publication guidelines will be established by the StrokeNet Steering Committee and the MOST Trial Publications Committee. Investigators are encouraged to publish and to publicly release and disseminate results, data and other products of the StrokeNet clinical trials as determined in collaboration with the Steering Committee. All publications must acknowledge the contributions of NINDS and the NIH StrokeNet. All affiliated study personnel are required to align with these procedures as outlined in StrokeNet SOP Number: ADM 03

2. Data Sharing

Because of the extensive effort that went into collecting data by investigators and study participants, it is important that datasets from completed studies be available for further research so that the full potential of the datasets is maximized. NDMC will submit to NINDS Office of Clinical Research a complete, cleaned, and de-identified dataset and any supporting documentation (including but not limited to the study protocol, statistical analysis plan, and data dictionary) required for the analysis of the data within one year of the primary publication or within 18 months of the last study visit of the last subject, whichever occurs first. For more information, see the NIH guidelines on sharing research data (http://grants.nih.gov/grants/policy/data_sharing/).

Specific data sharing policies will be developed in accordance with NINDS policy and NIH Guidelines. At the conclusion of each trial, the data will be put in a form suitably formatted for deposit in a national archive. The data will be made publicly available as determined by the Steering Committee with NINDS approval.

Y. MOP MAINTENANCE

The responsibility for maintenance of the MOP belongs to the Protocol Principal Investigator (PPI) or designee with assistance from the NCC and NDMC, along with any necessary protocol specific training modules and study document templates. Each version of the MOP will display the version number and date on the title page, as well as to what version and date of the protocol the MOP corresponds. Any updates to the MOP will be announced and made available via WebDCU™.

APPENDIX 1

Study Drug Compatibility

The following medications are either compatible or incompatible with MOST study drug when administered through the same IV site.

MOST Study Drug Y-site Compatibility Chart			
Drug	**Argatroban**	**Eptifibatide**	**Placebo**
Alteplase	**Incompatible***	Compatible via Y-Site	Compatible via Y-Site
Tenecteplase **	**Incompatible**	**Incompatible**	**Incompatible**
Dexmedetomidine	Compatible via Y-Site	**Incompatible**	Compatible via Y-Site
Etomidate	**Incompatible**	**Incompatible**	Compatible via Y-Site
Hydralazine hydrochloride	Compatible via Y-Site	**Incompatible**	Compatible via Y-Site
Ketamine hydrochloride	**Incompatible**	**Incompatible**	Compatible via Y-Site
Propofol	**Incompatible**	**Incompatible**	Compatible via Y-Site
Fentanyl citrate	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
Labetolol hydrochloride	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
Midazolam hydrochloride	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
Nicardipine hydrochloride	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
Rocuronium	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
Succinylcholine chloride	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
Vecuronium bromide	Compatible via Y-Site	Compatible via Y-Site	Compatible via Y-Site
*Argatroban may be administered through the alteplase IV line once the **alteplase infusion has been completed** and the line is flushed with 0.9% sodium chloride			
**Tenecteplase should be administered via a dedicated IV line in which no other medications are being simultaneously injected or infused			