NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

MOST

MOST Protocol Training

Current Protocol v5.2

University of CINCINNATI

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

UTHealth The University of Texas Health Science Center at Houston

MEMORIAL HERMANN Texas Medical Center

UNIVERSITY OF IOWA HEALTH CARE

Goals

- MOST protocol overview
- Familiarization with trial design, study interventions, enrollment process and follow-up procedures

Adjunctive Treatments to Thrombolysis

Six Phase 2 trials completed (CLEAR and ARTSS Trials)

Medications

- Eptifibatide - Platelet inhibition
- Argatroban - Thrombin inhibition

The best available evidence for adjunctive medications that combined with alteplase or tenecteplase may:

- Augment thrombolysis
- Prevent re-occlusion
- Result in improved outcomes over standard IV alteplase or tenecteplase

MOST Study Aim and Primary Endpoints

- **Study Aim:** Confirm safety and establish efficacy of IV thrombolysis plus IV argatroban OR IV rt-PA plus IV eptifibatide over standard IV **thrombolysis** alone for acute ischemic stroke

- **Primary Efficacy Endpoint:** 90-day functional outcome as measured by the modified Rankin Scale (mRS)

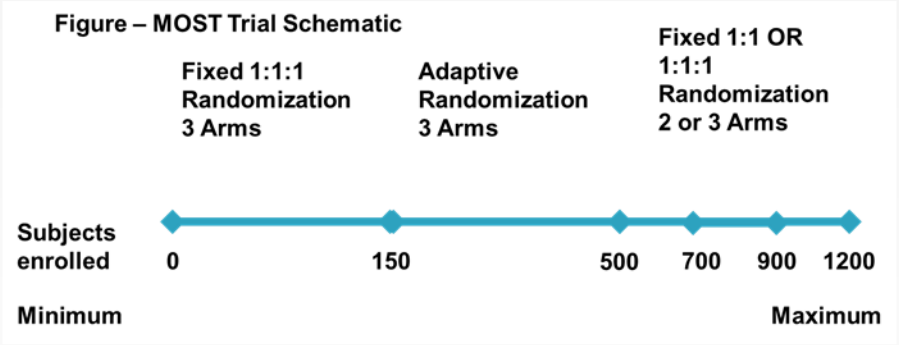
- **Primary Safety Endpoint:** Symptomatic Intracranial Hemorrhage (sICH) rate within 36 hours from randomization (overall and ET-specific)

Study Design

Study Drug Arms:

Study Arm	Bolus	0-2 hour infusion	2-12 hour infusion
Argatroban	100µg/kg	3µg/kg/ min	3µg/kg/ min
Eptifibatide	135µg/kg	0.75µg/kg/ min	placebo
Placebo	placebo	placebo	placebo

Randomization Scheme:



- Central randomization in WebDCU™
- Futility testing will occur at 500 subjects, and a futile arm may be dropped or the trial may stop if both futile
- Minimum of 500 subjects, maximum of 1200 subjects

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Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Acute ischemic stroke patients
2. 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
3. Age ≥ 18
4. NIHSS score ≥ 6 prior to IV thrombolysis
5. Able to receive assigned study drug within 60 minutes but no later than 75 minutes of initiation of IV thrombolysis

Exclusion Criteria:

1. Known allergy or hypersensitivity to argatroban or eptifibatide
2. Previous stroke in the past 90 days
3. Previous intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arterial venous malformation
4. Clinical presentation suggested a subarachnoid hemorrhage, even if initial CT scan was normal
5. Any surgery, or a biopsy of parenchymal organ in the past 30 days
6. Trauma with internal injuries or ulcerative wounds in the past 30 days
7. Severe head trauma in the past 90 days
8. Systolic blood pressure persistently >180mmHg post-IV thrombolysis despite antihypertensive intervention
9. Diastolic blood pressure persistently >105mmHg post-IV thrombolysis despite antihypertensive intervention10. Serious systemic hemorrhage in the past 30 days
11. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR >1.5
12. Positive urine or serum pregnancy test for women of child bearing potential
13. Glucose <50 or >400 mg/dl
14. Platelets <100,000/mm3
15. Hematocrit <25 %
16. Elevated pre-thrombolysis PTT above laboratory upper limit of normal
17. Creatinine > 4 mg/dl
18. Ongoing renal dialysis, regardless of creatinine
19. Received Low Molecular Weight heparins (such as Dalteparin, Enoxaparin, Tinzaparin) in full dose within the previous 24 hours
20. Abnormal PTT within 48 hours prior to randomization after receiving heparin or a direct thrombin inhibitor (such as bivalirudin, argatroban, dabigatran or lepirudin)
21. Received Factor Xa inhibitors (such as Fondaparinaux, apixaban or rivaroxaban) within the past 48 hours
22. Received glycoprotein IIb/IIIa inhibitors within the past 14 days
23. Pre-existing neurological or psychiatric disease which confounded the neurological or functional evaluations e.g., baseline modified Rankin score >3
24. 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
    a. Example: known cirrhosis or clinically significant hepatic disease
25. Current participation in another research drug treatment or interventional device trial - Subjects could not start another experimental agent until after 90 days
26. Informed consent from the patient or the legally authorized representative was not or could not be obtained
27. High density lesion consistent with hemorrhage of any degree
28. 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

Notable I&E

Inclusion Criteria

1. IV thrombolysis within 3 hours of LSN
2. Age ≥ 18
3. Pre IV thrombolysis NIHSS ≥ 6
4. Able to receive assigned study drug within 60 minutes but no later than 75 minutes of initiation of IV thrombolysis

Exclusion Criteria

1. INR >1.5 in patients on warfarin
2. Elevated pre-thrombolysis PTT (above local lab limit)
3. mRS >3
4. Large (>1/3 of MCA) clear CT hypodensity
5. Creatinine >4 or dialysis
6. Significant liver disease or known bleeding diathesis

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

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Acute Enrollment Period

- Every effort should be made to administer study drug within 60 minutes of IV thrombolysis bolus and **should not be administered** more than 75 minutes after IV thrombolysis bolus

- How to efficiently conduct MOST enrollment activities within protocol-defined time window?
  - Collaboration with Clinical Teams
  - Start Consent Conversation Early
  - Notify Pharmacy as Soon as Possible

WebDCU | MOST | Subject CRF

Jordan ELM

Edit: F102 Randomization

CRF ID: 171		F102 Randomization		Rule Status:
Site: 2347 WebDCU Test Site 1, Charleston, SC	Subject: 1001	Visit: Baseline/Randomization	Submit:	Accept:

No.	Item Description	Data Value
	Important Instructions: Randomization is irreversible. Please check all data items carefully and only click "Submit CRF" if you are ready randomize, treat, and follow the subject.	
	Before this form can be submitted and a randomized treatment assigned to this subject, the Subject Enrollment form must be submitted.	
	Important: Only patients treated with rt-PA within 3 hours of symptom onset or last seen well are eligible to be randomized. Patients must receive assigned study drug within 60 minutes of initiation of	
	A. Eligibility confirmation for randomization and dosing covariates	
A01	Subject meets all inclusion/exclusion criteria on Form 101	○ No ◉ Yes
A02a	Weight	85
A02b	Weight units	◉ kg ○ lb
A03	Endovascular therapy planned per usual care at the time of randomization	◉ No ○ Yes
	B. Baseline covariates adjusted by randomization algorithm	
B01a	NIH Stroke Scale score prior to IV rt-PA	8
	C. Randomization Results	
C01	Assigned drug kit ID *Assigned by WebDCU*	
Qc	General Comments:	*char.)*

Save Record

Cancel Edit

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

CRF ID: 171		F102 Randomization		Rule Status:	DCR:
Site: 2347 WebDCU Test Site 1, Charleston, SC	Subject: 1001	Visit: Baseline/Randomization	Submit:	Accept:	Verify:

No.	Item Description	Data Value
	Important Instructions: Randomization is irreversible. Please check all data items carefully and only click "Submit CRF" if you are ready randomize, treat, and follow the subject. *Before this form can be submitted and a randomized treatment assigned to this subject, the Subject Enrollment form must be submitted.* *Important: Only patients treated with rt-PA within 3 hours of symptom onset or last seen well are eligible to be randomized. Patients must receive assigned study drug within 60 minutes of initiation of IV rt-PA.*	
	A. Eligibility confirmation for randomization and dosing covariates	
A01	Subject meets all inclusion/exclusion criteria on Form 101	○ No ◉ *Yes*
A02a	Weight	85
A02b	Weight units	◉ *kg* ○ lb
A02	Weight in Kg *Derived from A02a and A02b*	85
A03	Endovascular therapy planned per usual care at the time of randomization	◉ *No* ○ Yes
	B. Baseline covariates adjusted by randomization algorithm	
B01a	NIH Stroke Scale score prior to IV rt-PA	8
B02	Age *Derived from Subject Enrollment*	35 *years*

WebDCU | MOST

Help

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

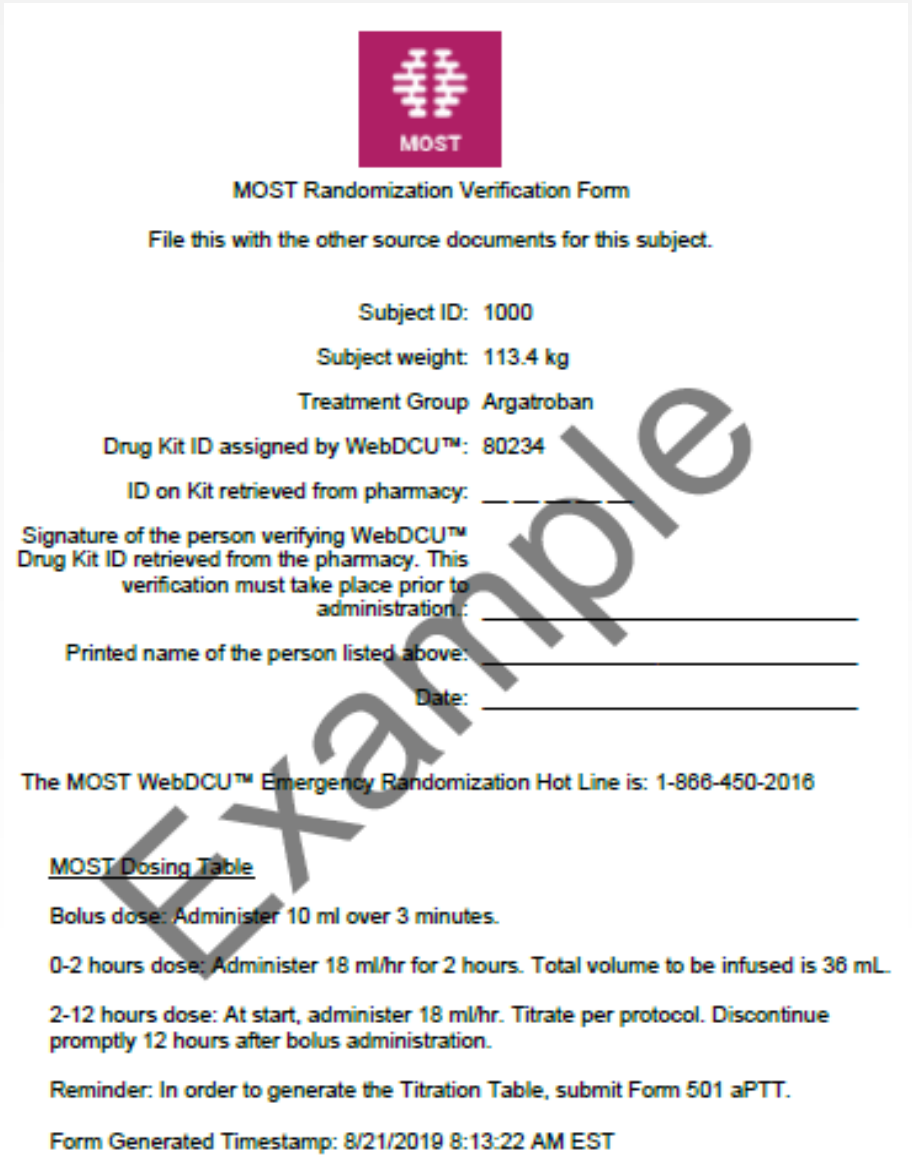
CRF ID: 171		F102 Randomization		Rule Status:	DCR:
Site: 2347 WebDCU Test Site 1, Charleston, SC	Subject: 1001	Visit: Baseline/Randomization	Submit:	Accept:	Verify:

No.	Item Description	Data Value
	Important Instructions: Randomization is irreversible. Please check all data items carefully and only click "Submit CRF" if you are ready randomize, treat, and follow the subject. *Before this form can be submitted and a randomized treatment assigned to this subject, the Subject Enrollment form must be submitted.* *Important: Only patients treated with rt-PA within 3 hours of symptom onset or last seen well are eligible to be randomized. Patients must receive assigned study drug within 60 minutes of initiation of IV rt-PA.*	
	A. Eligibility confirmation for randomization and dosing covariates	
A01	Subject meets all inclusion/exclusion criteria on Form 101	○ No ◉ *Yes*
A02a	Weight	85
A02b	Weight units	◉ *kg* ○ lb
A02	Weight in Kg *Derived from A02a and A02b*	85
A03	Endovascular therapy planned per usual care at the time of randomization	◉ *No* ○ Yes
	B. Baseline covariates adjusted by randomization algorithm	2646
B01a	NIH Stroke Scale score prior to IV rt-PA	8
B02	Age *Derived from Subject Enrollment*	72

John Smith
April 24, 2019

Click arrow to print.

MOST Randomization Verification Form



MOST

MOST Randomization Verification Form

File this with the other source documents for this subject.

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 WebDCU™ Emergency Randomization Hot Line is: 1-866-450-2016

MOST Dosing Table

Bolus dose: Administer 10 ml over 3 minutes.

0-2 hours dose: Administer 18 ml/hr for 2 hours. Total volume to be infused is 36 mL.

2-12 hours dose: At start, administer 18 ml/hr. Titrate per protocol. Discontinue promptly 12 hours after bolus administration.

Reminder: In order to generate the Titration Table, submit Form 501 aPTT.

Form Generated Timestamp: 8/21/2019 8:13:22 AM EST

Example

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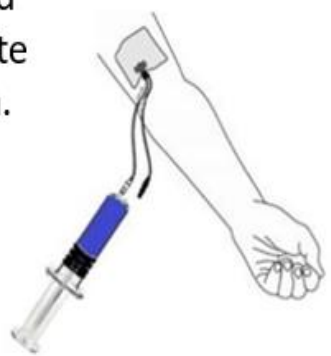
Study Drug Kit

Study Drug Arms:

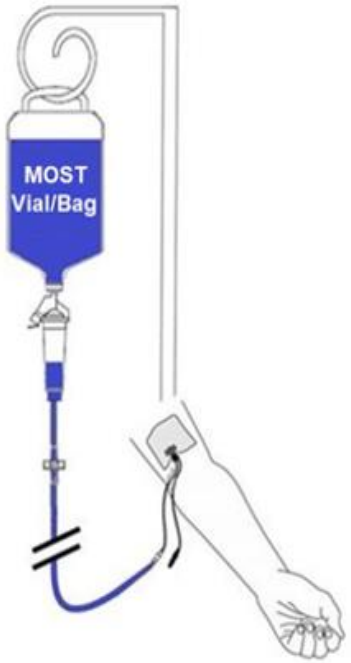
Study Arm	Bolus Dose	0-2 hour Dose	2-12 hour Dose
Argatroban	100µg/kg	3µg/kg/ min	3µg/kg/ min
Eptifibatide	135µg/kg	0.75µg/kg/ min	placebo
Placebo	placebo	placebo	placebo

Study Drug Administration

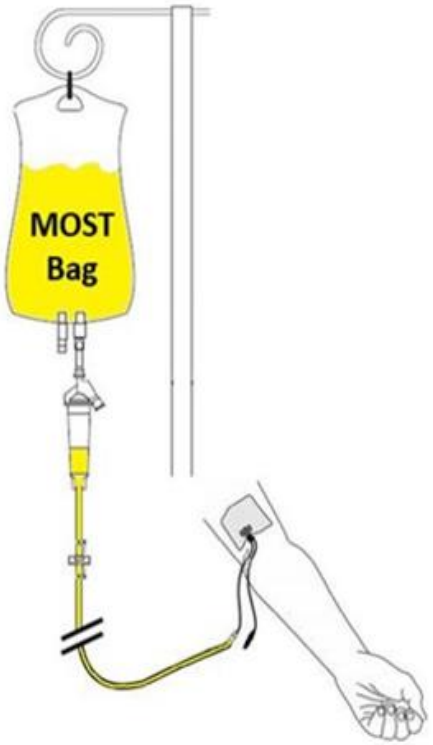
Bolus Dose:
Specific dose taken from infusion 1 vial/bag prepared and dispensed by pharmacy. Administered over 3-minute slow IV push.



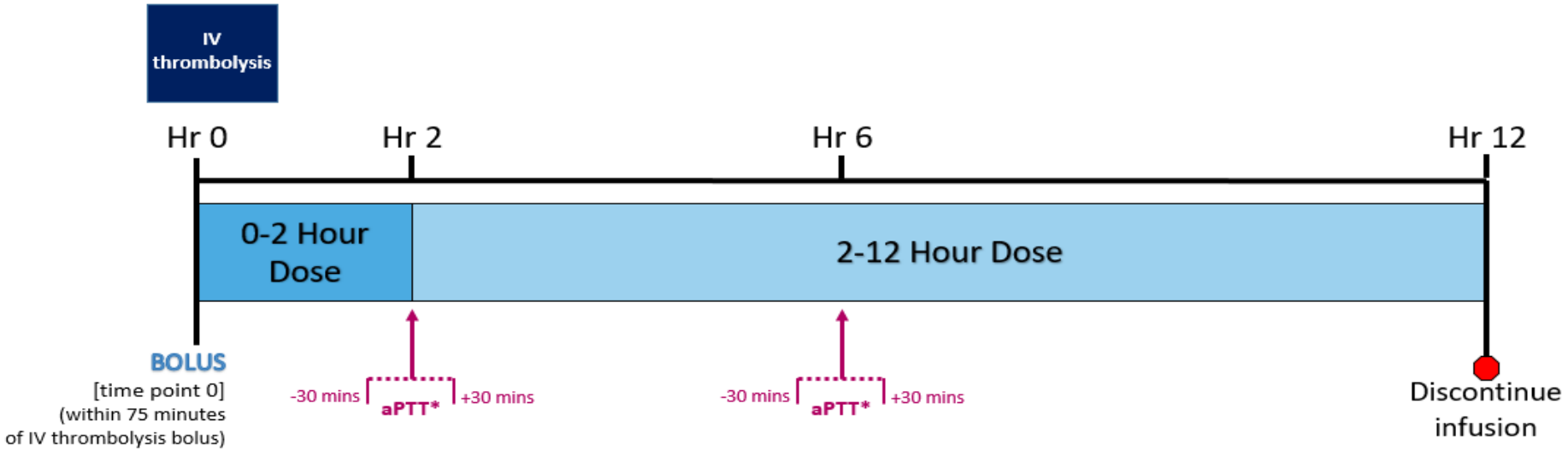
0-2 Hour Dose:
100ml vial/bag hung immediately after bolus for 2 hours at the rate indicated on Randomization Verification Form.



2-12 Hour Dose:
250ml bag hung immediately after 0-2 hour infusion dose until 12 hours after the bolus. Titrate at 2 hours and 6 hours for argatroban participants only.



Study Drug Administration & Argatroban Titration



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

View: F501 aPTT

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).

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).

Study Drug Administration Summary

Dosing Information is populated on Randomization Verification Form after entering subject weight on Randomization CRF

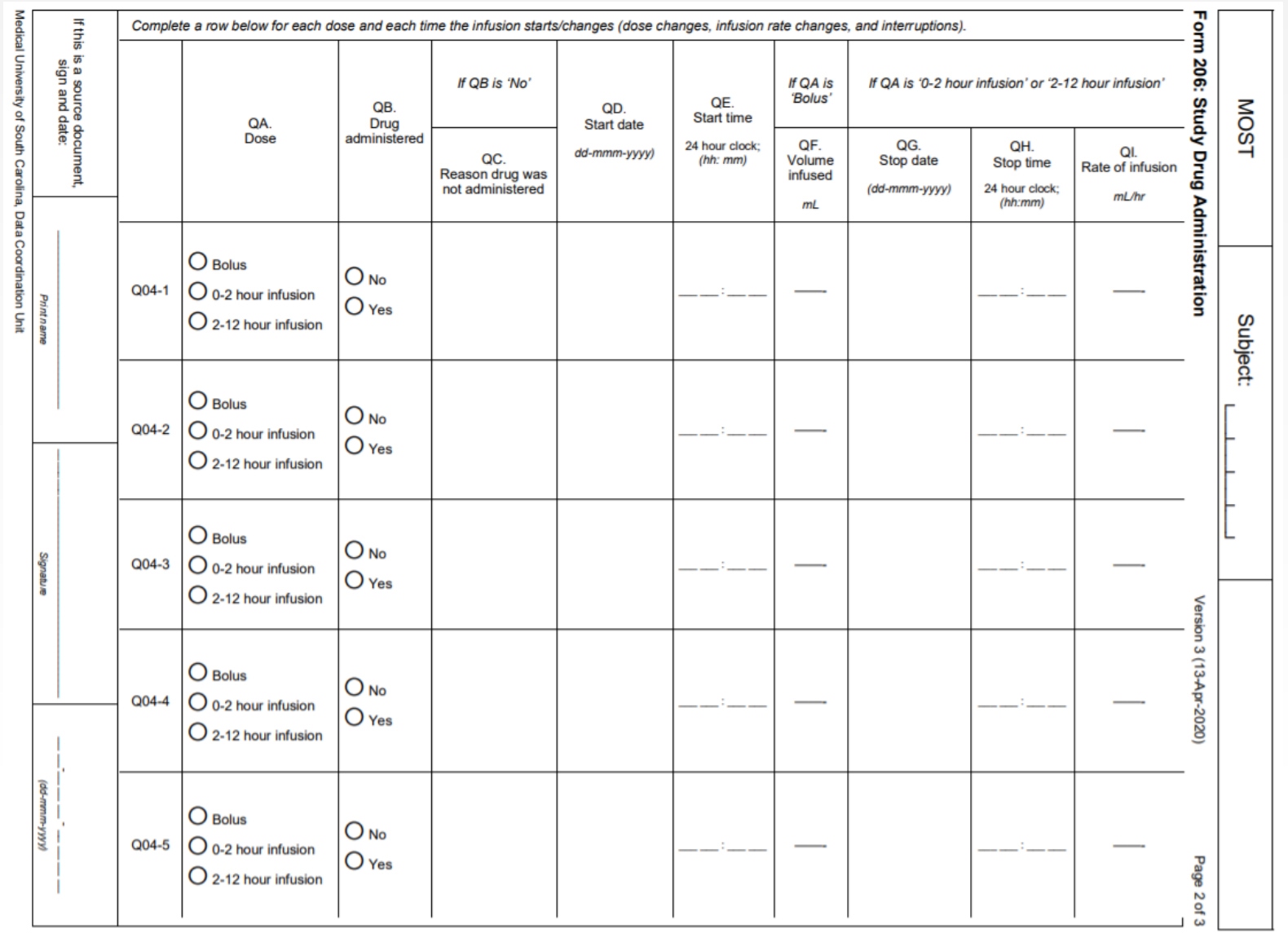
Bolus Dose
- Pulled from the 100ml vial/bag
- Administered over 3 minute IV push

0-2 Hour Dose
- 100ml vial/bag hung immediately after bolus
- Runs for 2 hours

2-12 Hour Dose
- 250ml bag hung immediately after 0-2 Hour Dose
- Runs until 12 hours after study drug bolus

Argatroban Only
- Titrate at 2 and 6 hours
- Titration information populated on aPTT CRF after entering baseline aPTT value

Study Drug Administration Documentation



Medical University of South Carolina, Data Coordination Unit

If this is a source document, sign and date:

Print name

Signature

(dd-mmm-yyyy)

Form 206: Study Drug Administration Version 3 (13-Apr-2020) Page 2 of 3

MOST Subject: ____

Complete a row below for each dose and each time the infusion starts/changes (dose changes, infusion rate changes, and interruptions).

	QA. Dose	QB. Drug administered	*If QB is 'No'* QC. Reason drug was not administered	QD. Start date *dd-mmm-yyyy*	QE. Start time 24 hour clock; *(hh: mm)*	*If QA is 'Bolus'* QF. Volume infused *mL*	*If QA is '0-2 hour infusion' or '2-12 hour infusion'* QG. Stop date *(dd-mmm-yyyy)*	QH. Stop time 24 hour clock; *(hh:mm)*	QI. Rate of infusion *mL/hr*
Q04-1	○ Bolus ○ 0-2 hour infusion ○ 2-12 hour infusion	○ No ○ Yes			__:__	____		__:__	____
Q04-2	○ Bolus ○ 0-2 hour infusion ○ 2-12 hour infusion	○ No ○ Yes			__:__	____		__:__	____
Q04-3	○ Bolus ○ 0-2 hour infusion ○ 2-12 hour infusion	○ No ○ Yes			__:__	____		__:__	____
Q04-4	○ Bolus ○ 0-2 hour infusion ○ 2-12 hour infusion	○ No ○ Yes			__:__	____		__:__	____
Q04-5	○ Bolus ○ 0-2 hour infusion ○ 2-12 hour infusion	○ No ○ Yes			__:__	____		__:__	____

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Concomitant Drugs and Procedures

- Concomitant use of antiplatelet or anticoagulant medications is prohibited in the first 24 hours after initiation of IV thrombolysis per SOC guidelines

- If clinical team has strong justification for the use of antithrombotics, a non-contrast head CT must be obtained to assess safety prior to administration

- After 24 hours, antithrombotic use may proceed per standard of care

Endovascular Therapy

- MOST participants are eligible to receive standard of care endovascular therapy, which should not be delayed for study procedures
- Study drug administration may occur before or during the endovascular procedure; therefore, collaboration is critical
- Additional antithrombotics or thrombolytics during the procedure, other than heparinized saline flush, are protocol violations
- Proximal carotid artery stenting should be avoided, angioplasty alone is recommended.

Adverse Event Reporting

- Non-serious Adverse Events (AEs) will be reported from randomization through Day 3 or Discharge, whichever comes first

- AEs will be reported in WebDCU™ within 5 days of the site's awareness of the event

Serious Adverse Event Reporting

- All Serious Adverse Events (SAEs) will be reported from randomization through Day 90

- SAEs will be reported in WebDCU™ within 24 hours of the site's awareness of the event and must be followed for the duration of the study follow-up or until resolution, whichever comes first

Safety Outcomes

- Trial-specific Safety Outcomes include:
  - sICH within 36 hours of randomization
  - Proportion of participants with parenchymal hemorrhage types 1 (PH-1) and 2 (PH-2) within 36 hours of randomization
  - Any ICH on brain imaging within 36 hours of randomization
  - Major hemorrhage (requiring >2 units of packed red cells) other than intracranial hemorrhage within seven days of randomization
  - All-cause mortality within 90 days of randomization

Imaging

- All standard of care head imaging should be uploaded to the Imaging Collection CRF using ASPERA software in WebDCU™

- This includes all non-contrast CT, CTA, CTP, MRI, MRA, and MRP performed within 72 hours of symptom onset

Follow-up Assessments

- 24 hours (± 12 hours)
  - Blinded NIHSS
  - CT/MRI (SOC)
  - AE/SAE assessment
- Day 3/Discharge (± 24 hours)
  - Consent Experience Survey

    May be collected up to Day 30
  - AE/SAE assessment
- Day 30 (± 7 days)
  - mRS
  - SAE assessment

    May be in-person or over the phone
- Day 90 (± 14 days)
  - mRS (must be video recorded)
  - EQ-5D-5L
  - SAE assessment

    Must be in-person

90-Day mRS Primary Outcome

- Primary outcome is highly dependent upon blinded central adjudication therefore video recording of the 90-day mRS assessment is required
- Videos will be uploaded to Glasgow web portal within 2 weeks of 90-day visit completion
- Every effort should be made to avoid LTFU

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Thank you!

Please email MOST@uc.edu with questions

University of CINCINNATI

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

UTHealth The University of Texas Health Science Center at Houston

MEMORIAL HERMANN Texas Medical Center

UNIVERSITY OF IOWA HEALTH CARE