The Multi-arm Optimization of Stroke Thrombolysis (MOST) Trial

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MOST

Goals

- Discuss enrollment process and study logistics
- Answer questions from study teams

Adjunctive Treatments to rt-PA

Medications

- Argatroban - Thrombin inhibition
- Eptifibatide - Platelet inhibition
- Both previously combined with rt-PA as SPOTRIAS projects

Six Phase 2 trials completed (CLEAR and ARTSS Trials) - underpowered for efficacy, but analyses suggest a direction of effect in favor of the combination therapies over rt-PA

The best available evidence for adjunctive medications that combined with rt-PA may:

- Augment thrombolysis
- Prevent re-occlusion
- Result in improved outcomes over standard IV rt-PA

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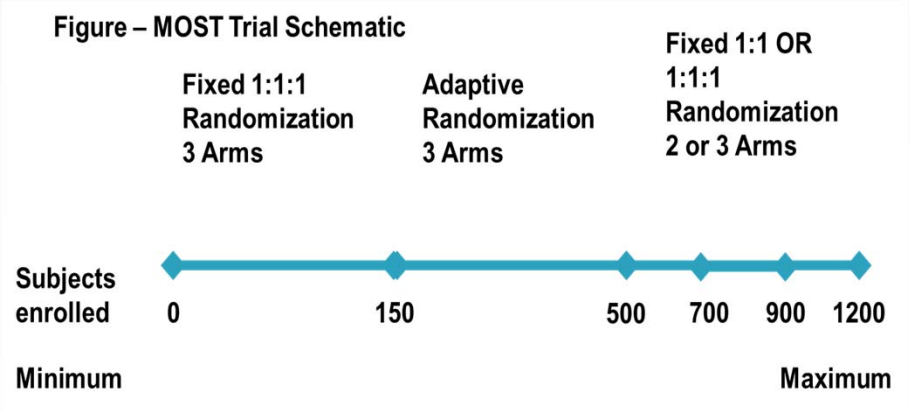
Multi-arm Optimization of Stroke Thrombolysis (MOST) Trial

- Study Drug Arms:

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

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

Placebo: bolus
0-2 hour infusion
2-12 hour infusion



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Inclusion and Exclusion

Inclusion Criteria:

1. Acute ischemic stroke patients
2. Treated with 0.9mg/kg IV rt-PA within 3 hours of stroke onset or time last known well
3. Age ≥ 18
4. NIHSS score ≥ 6 prior to IV rt-PA
5. **Able to receive assigned study drug within 60 minutes of initiation of IV rt-PA**

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. Surgery or 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 >180mmHg post-IV rt-PA
9. Diastolic blood pressure >105mmHg post-IV rt-PA
10. 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 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 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, eptifibatide or argatroban therapy was initiated
    a. Example: known cirrhosis or clinically significant hepatic disease
25. Current participation in another research drug treatment protocol - 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

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Schedule of Events

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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 ∞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 rt-PA administration and **should not be administered** 75 minutes after rt-PA

- How to efficiently conduct MOST consent, enrollment, randomization and treatment activities?
  - Early notification from stroke team and ED team
  - Identify family/LAR early
  - Defined pharmacy process

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Randomization and Study Drug Kits

- Randomization number will align with one study drug kit that is in inventory
- Each kit contains 3 vials corresponding to 1 of the 3 study arms and are labeled:
  - Vial 1: bolus (administer over 3 minutes)
  - Vial 2: 0-2 hour infusion (administer over 2 hours)
  - Vial 3: 2-12 hour infusion (administer over 10 hours and titrate per protocol)
- Randomization will require subject demographics, NIHSS, and weight
  - Weight-based dosing information will be provided on Randomization Verification Form

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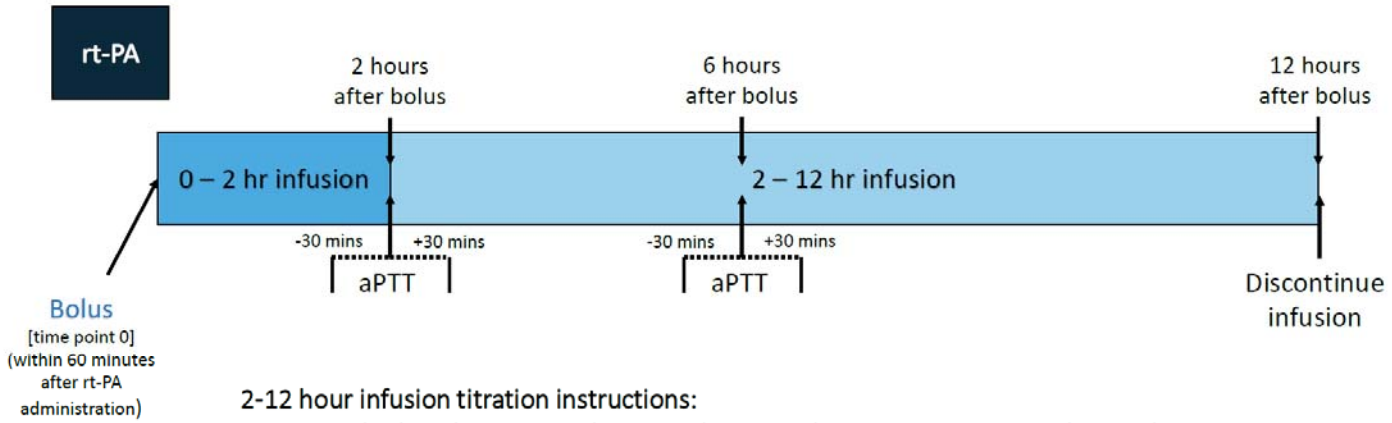
Study Drug Administration and Titration



2-12 hour infusion titration instructions:

1. Enter the baseline aPTT value in WebDCU under **Form 501 aPTT** and print the MOST Study Drug 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 the rate of the 2-12 hour infusion according to the titration table
4. Promptly at 12 hours after study drug bolus administration, discontinue the study drug infusion

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MOST Dosing and Titration Table

Vial 1 (Bolus)	Administer	8.5	ml over 3 minutes
Vial 2 (0-2 hrs)	Administer	15.3	ml/hr over 2 hours
Vial 3 (2-12 hrs)	At start, administer	15.3	ml/hr . Titrate per protocol

MOST Titration Table: Protocol to Target aPTT 2.25 x Baseline				
If the latest aPTT level is between		Then change the Flow Rate by (ml/hr) + or - the current flow rate		
<=	71.3	increase flow by	+	2.6
71.4	74.1	increase flow by	+	1.3
74.2	76.6	increase flow by	+	0.6
76.7	80.9	no change in flow		0.0
81.0	82.3	decrease flow by or by 50% of current rate if reduction would result in a rate of zero.		-0.6
82.4	86.5	decrease flow by or by 50% of current rate if reduction would result in a rate of zero.		-1.3
86.6	109.9	decrease flow by or by 50% of current rate if reduction would result in a rate of zero.		-2.6
110	130	**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.		
>130		**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).		

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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 rt-PA 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 as usual

Endovascular Therapy

- Additional antithrombotics or thrombolytics during the procedure, other than heparinized saline flush, are protocol violations
- Intracranial stenting is a protocol violation
- Stenting of proximal carotid stenosis or occlusion should be avoided or delayed for at least 24 hours, if possible
  - If stent is required, oral antiplatelet agents may be started after completion of the study drug infusion

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Follow-up Assessments

- 24 hours (± 12 hours)
  - NIHSS
  - CT/MRI (SOC)
  - AE assessment
- Day 3/Discharge (± 24 hours)
  - Consent experience survey
  - AE assessment
- Day 30 (± 7 days)
  - mRS
  - AE assessment (SAEs only)
- Day 90 (± 14 days)
  - mRS (must be video recorded)
  - EQ-5D-5L
  - AE assessment (SAEs only)

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Questions?

General Information and Reminders

- Sleep Smart IV Meeting Feb 22, 2019
- Upcoming CREST Coordinators meeting May 2-3, 2019.
- Presenters for upcoming Meetings/Coordinators Calls.
- StrokeNet Network webinar will be in late February or March.
- StrokeNet National Meeting in-person meeting in the fall of 2019.
- RPPR and Carry-Over requests due.
- QAR due Jan 4th
- No call next month