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

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# Study Team

- **Principal Investigators:**
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  - Jim Grotta, Memorial Hermann Hospital, Houston
  - Joe Broderick, University of Cincinnati
  - Colin Derdeyn, University of Iowa
- **Clinical Coordinating Center –** University of Cincinnati
  - Lead Trial Coordinator – Iris Deeds
- **National Coordinating Center –** NIH StrokeNet
  - Project Manager – Teresa Murrell-Bohn
- **Data Management –** MUSC/WebDCU

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# Background

- IV rt-PA alone opens ~50% of occluded arteries; 14-34% reocclude leading to worse outcomes
- 50% of rt-PA treated ischemic stroke patients are disabled at three months
- Based on ET treated patients in published trials, 31% did not achieve good recanalization and 25% had persistent occlusion at 24 hours
- Adjunctive IV antithrombotic medications may augment rt-PA thrombolysis and reperfusion

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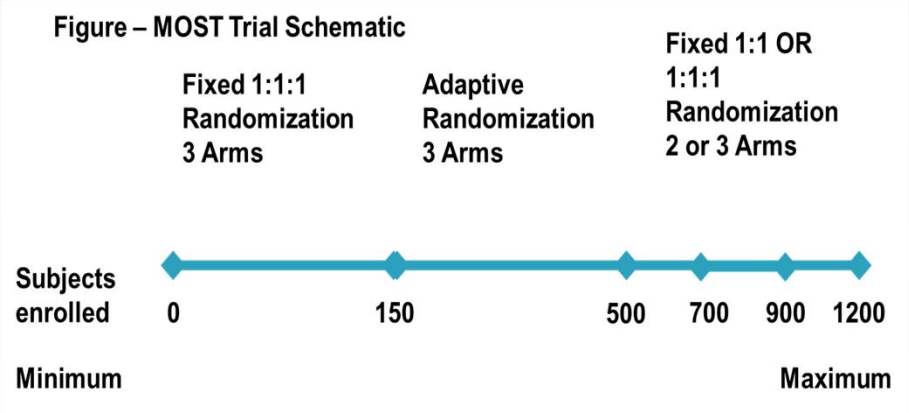
# Multi-arm Optimization of Stroke Thrombolysis (MOST) Trial

- 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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# Study Aim and Primary Endpoints

- **Study Aim:** Confirm safety and establish efficacy of IV rt-PA plus IV argatroban OR IV rt-PA plus IV eptifibatide over standard IV rt-PA alone for acute ischemic stroke
- **Primary Efficacy Endpoint:** 90-day functional outcome as measured by the mRS
- **Primary Safety Endpoint:** sICH rate (overall and ET-specific)

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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**

**Selected 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. Systolic blood pressure >180mmHg post-IV rt-PA
6. Diastolic blood pressure >105mmHg post-IV rt-PA
7. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR >1.5
8. Glucose <50 or >400 mg/dl
9. Platelets <100,000/mm3

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| Schedule of Events | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Time** | **Baseline** | **2 hour (± 30 mins) (after start of study drug)** | **6 hour (± 30 mins)** | **24 hour (± 12 hrs)** | **Day 3/Discharge (± 24 hrs)** | **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 |
| EQ-5D-5L | | | | X | | | X |
| CT/MRI scan (SOC#) | 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 ^serious AEs only ∞as needed based on aPTT titration protocol
** visit by phone or in-person ***in-person visit plus video recording of mRS

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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
  - Drip and Ships should be avoided

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# Study Drug Titration

- aPTT labs should be collected as early in the 2-hour (± 30 minutes) and the 6-hour (± 30 minutes) time windows as possible to allow time for the sample to be processed and resulted to determine if titration of the 2-12 hour infusion is indicated based on the MOST Dosing and Titration Table
  - aPTT collection outside of the time windows will be a protocol deviation

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# Clinical Fluctuation

- Study drug should be administered within 60 minutes of rt-PA in subjects eligible prior to rt-PA treatment even if there is clinical improvement or good recanalization before study drug administration Patients should not be randomized after 60 minutes from rt-PA administration
- Study drug should not be administered if there is clinical deterioration, e.g., BP not controlled within defined window, clinical suspicion for bleeding event

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# Infusion Interruptions

- If an infusion interruption occurs it should be restarted as quickly as possible if indicated/safe
- If the infusion is restarted, it should still be terminated promptly 12 hours after initial study drug administration
  - Ex: study drug bolus at 10:00am, study drug infusion termination will occur at 10:00pm regardless of interruptions
- If an interruption occurs during 0-2 hour infusion, the 0-2 hour infusion vial (vial 2) should be continued upon restarting
- Vials can be disposed of after use

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# Endovascular Therapy

- The clinical treatment process occurs independent of the study
  - The bolus could occur in the angio suite for some subjects or subjects with bolus prior to angio will come up with an additional (if tPA is still dripping) infusion of study drug
- If recanalization is achieved at any point during procedure, study drug should still be administered in full
- 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 at 12 hours AND no evidence of bleeding on head CT

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# AE Reporting

- Non-serious Adverse Events (AEs) that **are determined to be related** to study drug will be reported from randomization through Day 3 or Discharge, whichever comes first
- All Serious Adverse Events (SAEs) and all safety outcomes will be reported from randomization through Day 90

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# AE Reporting

- Study Drug related, non-serious adverse events will be reported in WebDCU™ within 5 days of the site's awareness of the event
- Serious Adverse Events 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
- For all reportable adverse events, Clinical Site Investigators will determine the AEs:
  - Grade/severity
  - Relationship to study drug
  - Seriousness

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# Follow-up Assessments

- 24 hours (± 12 hours)
  - NIHSS
  - CT/MRI (SOC)
  - AE assessment
- Day 3/Discharge (± 24 hours)
  - 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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# Current Status

- Primary rate-limiting step is study drug reconstitution and stability testing prior to FDA approval
- Anticipate FDA approval February 2019
- CIRB approval to follow soon after
- Open enrollment at first sites in March 2019

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