Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Grotta JC, Yamal J-M, Parker SA, et al. Prospective, multicenter, controlled trial of mobile stroke units. N Engl J Med 2021;385:971-81. DOI: 10.1056/NEJMoa2103879

This supplement contains the following items:

1. Summary of protocol changes, Original protocol, Final protocol.

2. The Statistical Analysis Plans versions 3.8 and 3.9. Version 3.8 is the same as the original SAP except for the changes over the course of the study and their dates as described on the first page. The final version of the SAP is version 3.9 which, as described on the first page, includes the additional analyses conducted in response to the NEJM review process.

SUMMARY OF PROTOCOL CHANGES

The original protocol, labelled 3/1/15, describes the conduct of the controlled alternating week trial from its inception at a single site (Houston), and anticipated completion of enrollment by 8/31/20. This original protocol included enrollment of 541 tPA eligible patients. It incorporated the same selection criteria for enrollment and determination of tPA eligibility, and the same study procedures including blinded adjudication for tPA eligibility and 90 day outcomes, as used throughout the rest of the study. The primary outcome for the first Specific Aim was the change in the mean utility weighted mRS from pre-stroke level to 90 days in tPA eligible patients. The secondary outcomes were the same as used throughout the rest of the study, namely, ordinal and categorical analyses of the mRS in tPA eligible and all tPA treated patients, hemorrhage, stroke mimics, mortality and time metrics. Specific aims two and three were to determine the accuracy and speed of telemedicine vs on-board assessment, and health care utilization and cost effectiveness analysis based on one-year follow up of all tPA eligible patients, respectively.

The next version of the protocol, dated 10/29/15, made three changes from the original protocol. These were the addition of the Memphis and Colorado sites, increase in sample size to 693 patients based on the projected additional enrollment at those sites, and allowing CTA on board the MSU in the MSU arm as long as it didn't delay tPA administration.

The next version of the protocol, dated 4/19/18 made several changes.

a. Los Angeles (UCLA), New York (NY Presbyterian), and Burlingame (Sutter-Peninsula) were added as sites.
b. The number of tPA eligible patients to be enrolled was increased to 1038 based on newly available data from the Berlin MSU as described in the Supplement (page 3). This sample size re-estimation was blinded to study outcomes, and also considered the numerical imbalance between the MSU and SM groups observed during the run-in phase and first part of the trial.
c. The end of patient enrollment was extended to 6/30/21 to accommodate the increased sample size.
d. The primary outcome was changed from change in mean uw-mRS from pre-stroke to 90 days to mean uw-mRS at 90 days.
e. Time limits around the various end-points were clarified, e.g. primary outcome at 90 days – 7d or + 30d.
f. The Houston catchment area was increased from 5 mi to 9 mi.
g. ICD-10 codes were added to the utility analysis (SA 3).
h. Clarification of the definitions of definite and possible relatedness of SAEs, and allowing reporting of SAEs up to 72 hours post event (had been 24 hrs).

The final version of the protocol, dated 9/18/19 allowed the addition of the Indianapolis site, but no other changes.

BEnefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study

Trial Synopsis

Trial No.:	HSC – MS- 13- 0322
Title:	**BE**nefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services:The **BEST-MSU** Study
Study Type:	Prospective cohort study with randomized deployment weeks and blinded assessment of both trial entry and clinical outcomes
Principal Investigator:	James Grotta, MD
Institute/ Department:	Memorial Hermann Hospital, Houston, Texas
Investigator:	James Grotta MD
Date of Protocol:	March 1, 2015
Planned Dates of Trial	Start: August 18, 2014 1, 2015 End: August 31, 2020

Objectives: The primary goal of this project is to carry out a trial comparing pre-hospital diagnosis and treatment of patients with stroke symptoms using a Mobile Stroke Unit (MSU) with subsequent transfer to a Comprehensive Stroke Center (CSC) Emergency Department (ED) for further management, to standard pre-hospital triage and transport by Emergency Medical Services (EMS) to a CSC ED for evaluation and treatment (Standard Management-SM).

There are many ways that use of a MSU might prove valuable in stroke patients, but we will focus on acute ischemic stroke (AIS) and treatment with IV tissue plasminogen activator (tPA) within 4.5 hours of symptom onset since that is the most evidence based effective emergency treatment for the most prevalent stroke diagnosis. **We hypothesize that the MSU pathway will produce an overall shift towards earlier evaluation and treatment, particularly into the first hour after symptom onset, leading to substantially better outcome. We will also explore the hypothesis that as a result of improved clinical outcomes resulting from earlier treatment, the costs of a MSU program will be offset by a reduction in the costs of long term stroke care and increase in quality adjusted life years,** thereby supporting more widespread use of this technology. To make MSU deployment more practical, **we will confirm that a Vascular Neurologist (VN) on board the MSU can be replaced by a remote VN connected to the MSU by telemedicine (TM)** thereby reducing manpower requirements and costs.

The successful completion of this project will provide data on important outcomes and costs associated with the use of MSU vs SM in the United States (U.S.) that will inform a “go” vs “no-go” decision to determine the value of integrating MSUs into the pre-hospital environment throughout the country. Therefore, the proposed study is the necessary first step in a process that may dramatically modify the way that acute stroke patients are managed.

No. of Clinical Sites: 1
No. of subjects:
To be assessed for eligibility (n = 5000)
To be enrolled (n = 1100)
To be analyzed ("tPA eligible") (n = 541)

Main criteria for inclusion:

1. Criteria for MSU team to **enroll** a patient into the study (to be determined pre-hospital on both MSU and SM weeks)

    a. Last seen normal possibly within 4hr 30 min

    b. History and physical/neurological examination consistent with acute stroke

    c. No definite tPA exclusions per guidelines, prior to CT scan or baseline labs

    d. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment, including IV tPA, will not be delayed for consent; however, consent in both MSU and SM patients must eventually be obtained for data to be retained for analysis.

2. Criteria for **tPA eligibililty** (to be determined pre-hospital on MSU weeks, and after ED assessment on SM weeks, and confirmed by blinded adjudication)

    a. Meeting tPA inclusion and exclusion criteria per guidelines after CT scan, baseline labs, and clinical re-evaluation

Test Procedure:	Pre-hospital diagnosis and treatment of patients with stroke symptoms using a MSU with subsequent transfer to a CSC ED for further management
Reference Procedure:	Pre-hospital triage and transport by EMS and treatment at a CSC ED

Primary endpoint:	1. Change in utility-weighted mRS from baseline to 90 days, comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks.
Secondary endpoints (in hierarchical sequence of importance):	2. The agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation. **N.B**. Patients will include all enrolled patients on MSU weeks considered for tPA treatment. 3. An exploratory cost-effectiveness analysis (CEA) of MSU versus SM using the Incremental Cost Effectiveness Ratio and Incremental Net Benefit estimate will be performed. **N.B**. The exploratory CEA will include all enrolled patients on MSU and SM weeks found eligible for

	tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) 4. a. Change in utility-weighted mRS from baseline to 90 days, b. ordinal (shift) analysis of mRS at 90 days, and c. proportion of patients achieving 90 day mRS 0,1 vs 2-6 of enrolled patients treated with tPA within 60 minutes of LSN onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS) between the groups at the time of treatment. **N.B**. Patients will include only those patients actually treated with tPA based on the final determination of the time LSN, and will include only patients meeting all inclusion and exclusion criteria. 5. a. ordinal (shift) analysis of mRS at 90 days, and b. proportion of patients achieving 90 day mRS 0,1 vs 2-6 comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks. 6. The time from LSN to tPA treatment on all patients treated within 4.5 hours of LSN on MSU weeks compared to similarly eligible patients on SM weeks. **N.B**. Patients will include all enrolled patients actually treated with tPA (or on SM weeks, eligible for tPA treatment) meeting all inclusion and exclusion criteria, and based on the final determination of time of LSN. One analysis will compare the median times. A second analysis will also capture the patients who were eligible but did not receive tPA because it was too late, categorizing time into the following groups (e.g., 0-60min, 61-90min, 91min-180min, 181-270min, eligible but no tmt because>270). 7. Of the enrolled patients that were eligible for treatment with tPA (according to published guidelines) on MSU weeks compared to SM weeks, the percent that were treated within 4.5 hours and within 60 minutes of LSN. 8. The time from LSN and from ED arrival to start of endovascular procedure (intra-arterial thrombectomy-IAT) in patients who meet pre-specified criteria for IAT on MSU weeks compared to SM weeks. **N.B.** All patients receiving IAT will be included in this outcome. 9. The median/mean time from LSN to tPA therapy decision on all patients considered for treatment within 4.5 hours of LSN on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patients meeting inclusion criteria whether or not treated with tPA.

	10. Time between 911 call and onset of etiology-specific BP management on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patients.
Safety endpoints	1. The incidence of symptomatic intracranial hemorrhage (sICH) in enrolled tPA treated patients on MSU weeks compared to SM weeks (Symptomatic intracranial hemorrhage defined as any intracranial blood accumulation associated with a clinical deterioration of $\geq$ 4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration) **N.B.** Patients will include all patients treated with tPA, whether or not they meet all inclusion and exclusion criteria. 2. Mortality. **N.B.** All enrolled patients signing informed consent will be included in this endpoint and followed until 1 year. 3. The incidence of stroke mimics and transient ischemic attacks (TIAs) in tPA treated patients on MSU weeks compared to SM weeks. **N.B**. SM patients deemed eligible for tPA on their pre-hospital assessment who then completely recover by the time of arrival in the ED will equal the excess incidence of TIAs treated on the MSU pathway.

Pre-Hospital data to be collected:

1. Dispatch time
2. Arrival on scene time
3. Last seen normal time
4. Enrollment time
5. Baseline labs
6. CT time
7. tPA decision time
8. tPA bolus time
9. tPA infusion start time
10. First Blood Pressure treatment time and BP readings q5 min
11. Departure time from scene
12. On scene time—time from MSU arrival to time of departure to hospital
13. Time of hospital arrival
14. Distance from emergency site to point of MSU dispatch and to destination ED
15. NIHSS at time of tPA treatment and on ED arrival
16. CT scan result

Visit	1	2	3	4	5	6	7	8	9	10
Hour/Day Window	Baseline(= 1st physician/ neurologist contact)	24 Hrs. ± 2 Hrs.	48 Hrs. ±12 Hrs.	72 Hrs. ±12 Hrs.	Day of Discharge	30 Days ± 7 days	90 Days ±14 Days	6 month follow up	9 month follow up	12 month follow up
Demographics	X									
Medical History	X						X			
In-/Exclusion Criteria	X									
Informed Consent and subject Information	X									
Vital Signs	X									
Thrombolysis as indicated	X									
Adverse Events	X	X	X	X			X			
CT Scan#	X##									
NIHSS	X	X			X		X			
Modified Rankin** Scale	X				X	X	X			
Pat. Termination Record							X			
Resource utilization information for cost analysis†	X				X		X	X	X	X
EQ-5D Form and Own Health Assessment Form					X		X	X	X	X

Fig.1 Flow Chart

Follow up CT or MRI imaging is optional as is the timing (except in ICH patients—see below). It will be carried out as per routine care and results will be recorded if done. CT or MRI will be immediately performed in the case of neurological deterioration.

In ICH patients, CT scan to be repeated after 1 hour in all MSU patients, and after 24 hrs in all MSU and SM patients

** Pre-stroke mRS will be determined; Telephone mRS ok at 30 days

† Details about all the resource utilization forms and quality of life measurement forms, and their timeline are provided in Table 1 below

Table of Contents

1. Specific Aims

The primary goal of this project is to carry out an exploratory trial comparing 1. pre-hospital diagnosis and treatment of patients with stroke symptoms using a Mobile Stroke Unit (MSU) with subsequent transfer to a Comprehensive Stroke Center (CSC) Emergency Department (ED) for further management, to 2. standard pre-hospital triage and transport by Emergency Medical Services (EMS) to a CSC ED for evaluation and treatment (Standard Management-SM). There are many ways that use of a MSU might prove valuable in stroke patients, but we will focus on acute ischemic stroke (AIS) and treatment with IV tissue plasminogen activator (tPA) within 4.5 hours of symptom onset since that is the most evidence based effective emergency treatment for the most prevalent stroke diagnosis.

Specific Aim 1: Compare outcome with MSU vs SM in tPA eligible patients

Determine if tPA eligible patients enrolled on randomized weeks when a MSU is available will have a significantly higher utility-weighted modified Rankin Scale (mRS) at 90 days after stroke onset, compared to patients enrolled on weeks when MSU was not available.

Rationale: MSU availability may lead to a significant shorter time to decision and treatment in a representative U.S. urban setting, leading to improved long-term outcome. Hypothesis: For patients calling 911 for suspected acute ischemic stroke, time from LSN to tPA bolus will be shorter in MSU weeks compared to SM weeks, leading to an improvement in the utility-weighted mRS at 90 days.

The primary outcome is the change in utility-weighted mRS (Δ uw-mRS) from baseline to 90 days in patients found eligible for tPA on MSU weeks compared to SM weeks. The uw- mRS assigns values to each mRS grade depending on patients' value of that level of function, with lower mRS scores (reflecting less disability) given proportionately higher weight than higher mRS scores (reflecting more disability).

Patients on MSU weeks vs SM weeks will also be compared for differences in secondary outcomes (a) time from LSN to tPA treatment, (b) the proportion of patients treated within 4.5 hours and within 60 minutes of LSN, (c) the time from LSN to start of endovascular procedure and the number of patients receiving IAT, (d) time from LSN to tPA therapy decision, and (e) time from 911 call to onset of etiology-specific BP management, and safety outcomes (i) incidence of symptomatic intracranial hemorrhage,(ii) mortality, and (iii) incidence of treated stroke mimics and TIAs. We will also compare the 90 day mRS in patients treated with tPA within 60 minutes of LSN, regardless whether they enrolled in an MSU or SM week, compared with patients treated 61-270 minutes.

Specific Aim 2: Determine the agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation.

Rationale: One of the main drivers of MSU costs and availability will be the added manpower needed to assess and treat the patient in the field. We will evaluate TM accuracy and reliability for the use of tPA in the MSU setting. Hypothesis: > 90% agreement between on-site and remote tPA decision-making, and > 90% consults completed without technical failures.

Specific Aim 3: Determine the incremental cost and effectiveness associated with the MSU vs SM using exploratory cost-effectiveness analyses.

a) Determine the cost-effectiveness of the MSU intervention from the perspective of healthcare payers under current reimbursement policies with no additional reimbursement for MSU dispatch.
b) Determine the cost-effectiveness of the MSU intervention from the perspective of healthcare payers if agencies and providers receive additional reimbursement for incremental MSU-related fixed costs per patient.

Rationale: Better outcomes among patients transported by the MSU and receiving timely tPA treatment might save costs for healthcare payers due to lower post-stroke utilization of healthcare services. However, these cost savings associated with post-stroke utilization have to be considered in combination with the incremental fixed costs of introducing and operating an MSU. These fixed costs imply that the agency operating the MSU requires additional reimbursement to ensure the financial viability and sustainability of the operation. Also, the provider supporting TM

management should also be reimbursed for their services. Hence a cost analysis, aimed to provide an economic basis for higher reimbursements for MSU dispatch, is a critical component of the intervention evaluation in this trial. The investigators realize that the stroke management and post-stroke management cost in the MSU group might be larger than the SM group. This could be due to increased death rates in the SM group (as a result of delayed or no tPA admisnitration after stroke in the SM group). Hence the final analysis might not demostrate cost-savings but could still demostrate a significant increase in QALY (capturing both length of survival and quality of survival) for the MSU group. Higher QALY will also be supportive of the MSU intervention depending on the incremental increase in cost per additional QALY.

2. Significance and Biologic Relevance

Intravenous tPA remains the only Level 1A treatment for AIS based on several prospective randomized trials comparing tPA to standard treatment.[1] The results of these trials and of pooled analyses confirm the relationship of treatment success with time from symptom onset to initiation of treatment.[2-7] However, despite two decades of efforts to streamline systems of care most patients are treated beyond the first 2 hours during which tPA is most effective.[8] While there are many reasons for this delay, one reason is an inherent delay caused by ED triage, registration, evaluation, testing, and treatment. The median door to needle times in stroke center EDs in the U.S. approximates 60 minutes.[9] Such delay not only likely results in less patients completely recovering, but reduces the total number of patients who can be treated within the 4.5 hour maximum time window of tPA effectiveness, contributing to the overall low national treatment rate estimated to be about 5% of all AIS.

Recently, the long awaited concept of faster pre-hospital treatment with tPA has become a reality following the demonstration by two groups in Germany that CT scanners can be mounted on an ambulance and treatment "taken to the patient". Walter et al showed that, using this MSU concept, treatment with tPA can be carried out safely and accurately with a median LSN to treatment time of 70-80 minutes.[10] Ebinger et al showed that a MSU, compared to SM, resulted in increased treatment rates (from 21% to 33%), 25 min shorter time to treatment, and increased proportion of patients treated within 90 minutes of symptom onset (58% vs 37%).[11]

This success has the potential to result in substantially improved outcomes for patients with AIS, and dramatically modify the way that acute stroke patients are managed. However, there are many gaps in our knowledge that need to be addressed before stroke systems of care in the U.S. should be modified to include the MSU concept. These gaps will be addressed by our Specific Aims.

Our primary aim is to begin to explore the question of whether patients eligible for tPA in the pre-hospital setting have better outcome if managed via a MSU or by SM. This will be accomplished by an intention-to-treat analysis that will include all eligible patients (whether or not they eventually receive tPA) evaluated at the same time in the prehospital setting, and by the same personnel, in both the MSU and SM groups. Assessing and enrolling all patients while they are still in the pre-hospital phase, and adjudicating their qualifications by a vascular neurologist (VN) blinded to MSU vs SM who will review the clinical information without data that would reveal MSU vs SM will assure that SM patients that are enrolled are comparable to the MSU patients, and will also allow us to account for those patients who would have met criteria for pre-hospital treatment but could not be treated within the 4.5 hour time window because they were managed on the SM pathway.

MSU management might result in better outcomes from tPA treatment by achieving faster treatment. There is no experience using the MSU in the U.S., so we do not know how much time can be saved by use of MSUs in the U.S. where traffic patterns, distances, market forces, and local regulations differ from Europe. Certainly, the impact of any change in a stroke system of care such as MSU deployment will be location-specific and differ between urban and rural areas.

Faster treatment using the MSU will allow us for the first time to answer an important scientific question by making treatment possible within the first 60 minutes after LSN when tPA is likely

to have its greatest impact. 31% of patients treated with tPA using the Berlin MSU were treated within 60 minutes of LSN compared to 4.9% with SM[12]. Among the 302 patients treated within 90 minutes of onset with tPA vs placebo in the NINDS study[2], only 2 were randomized within 60 minutes of LSN (both were randomized to the placebo group), and 41 were randomized between 61-80 minutes after onset (unpublished data from NINDS Stroke Study). Of 65,384 patients treated with tPA in the Get With the Guidelines Stroke Program, only 878 (1.3%) were treated within 60 minutes of LSN[13]. There is even less information on how much improvement in clinical outcome will occur with treatment within the first 60 minutes. While data from multiple studies and pooled analyses confirm a strong inverse relation between time to treatment and recovery, the slope and shape of that relationship within the first 90 minutes after LSN is very uncertain as reflected in the wide confidence intervals surrounding outcomes in various pooled analyses, and the total absence of data < 60 minutes. It is possible that, due to collateral flow, human penumbral tissue can survive long enough so that within the 90 minute epoch, there would be little advantage to earlier treatment. However, the Berlin group found that patients treated within the first 60 minutes of LSN by their MSU had an OR of 1.93 (95% CI 1.09-3.41) of discharge to home compared to later treatment[12], and in the GWTG database patients treated within 60 minutes of LSN showed an OR of 1.72 (1.21-2.46) for discharge mRS 0,1 compared to 61-270 min[13]. Our study will determine the benefit of tPA on long term outcome in prospectively studied patients treated within 0-60 vs 61-270 minutes.

There are several potential complexities with earlier treatment on the MSU which will also be addressed by our study. One is the increased chance of treating stroke mimics, e.g. patients with other pathologies such as migraine or seizures, or patients with TIAs, e.g. patients who would recover within 24 hours even without treatment. Regarding stroke mimics, Ebinger et al reported the rate of stroke mimic treatment with MSU to be 2%, and no different than with SM[11]. During weeks randomized to SM, we will evaluate all patients who we determine would have met criteria for treatment during the pre-hospital interval (X) but who then completely recover by the time of tPA decision in the ED (Y). We will consider Y/X as an approximation of the percentage of "TIA" treated patients in the cohort of tPA treated patients with MSU dispatch.

Another objective of our study is to determine the impact of MSU deployment on Intra-Arterial Thrombectomy (IAT). Recent trials have shown a benefit for IAT as an adjunctive approach to tPA in patients with severe strokes and persisting large artery occlusion after tPA[14-17]. All these studies, as well as post-hoc analysis from IMS-III[13] emphasize the benefits of quicker treatment and coordination among the multidisciplinary care team including pre-hospital triage to endovascular centers. MSU deployment might enable more accurate and rapid identification of IAT candidates and potently reduce time to IAT treatment, perhaps allowing bypass of ED evaluation altogether.

Eventually, the widespread use of MSUs will depend on adequate manpower to guide treatment. Our preliminary experience, and data from Germany, suggest that the ratio of MSU "alerts" from EMS dispatch to tPA treatments is at least 10:1 making it impractical to have a VN on board the MSU for all calls. However, the decision whether to give tPA based on clinical criteria requires training, experience, and careful judgment. Recently, we have demonstrated the feasibility and accuracy of TM assessment of actors simulating stroke patients in ambulances using existing technology [19]. However, **TM has not been tested for treating actual stroke patients with tPA in the pre-hospital environment**. By simultaneous TM evaluation of the stroke patient on-scene using a monitor mounted on the MSU gurney and facilitated by the MSU paramedic, we will compare the diagnostic and tPA-related treatment decisions made by the on-scene VN to those made by a VN at the hub assessing the patient via TM. We will also measure the rate of technical failures in conducting the TM consultation.

Economic Impact of Stroke: Stroke is among the top 15 most expensive conditions treated in the US hospitals, and among the top 10 most expensive conditions billed to Medicare.[20,21] Medicare bears the highest cost burden of the disease; almost 60% of stroke-related hospital costs and more than 60% of overall stroke-related costs are borne by Medicare. [21,22] Non-nursing home stroke care constitutes more than 10% of Medicare's budget [23]. As the US population ages, the incidence and prevalence of this disease will increase, and hence costs associated with stroke and the cost burden of Medicare will substantially increase. It is projected that by 2030 4% of the American population would have had a

stroke and the total medical cost of stroke will be nearly $200 billion (2010$), which is a 250% increase as compared to the medical costs as of 2012. [24]

Economic evaluation of tPA: Ischemic stroke accounts for 87% of all stroke events. The early use of tPA has been shown to be both clinically efficacious and cost-effective. Fagan et al [25] demonstrated that the use of tPA (as compared to placebo) reduced hospital length of stay, with higher discharge to homes instead of inpatient rehabilitation or nursing homes. Their Markov analysis predicted an increase in quality adjusted life years (QALYs) with 94% probability and a decrease in post-stroke first year costs with 93% probability among patients receiving tPA. In another study, tPA use within 4.5 hours of stroke occurrence had an ICER of $1478/QALY (in Australian currency) during the first year but also marginally increased costs[26]. Tung et al [27] performed a life-time cost effectiveness analysis for the use of tPA and found an increase in both life-time costs and QALYs with tPA administered within 4.5 hours of ischemic stroke, with an ICER of $21,978/QALY.

In spite of the benefits associated with tPA, the drug is used in a very small proportion of stroke patients [28,8,9] because of the small window of opportunity for its administration. Demaerschalk et al [28] showed that if tPA was used in 20% of stroke patients it would save $74 million in medical costs during the first year after the stroke event. This amount is 10 times more than the amount saved with the current tPA use of 2-4%. The technology proposed in our study strives to reduce the time from stroke onset to treatment initiation thereby increasing the probability of tPA administration among ischemic stroke patients.

While the literature provides ample evidence on the economic impact of stroke and cost-effectiveness of tPA, there are no studies within the US, which specifically evaluate the economic impact of an MSU using telemedicine capabilities to improve early tPA administration. This study aims to address this gap and is the first in the nation to perform an exploratory economic evaluation of this technology.

Significance of the Cost Analysis: The MSU intervention is geared towards improving clinical outcomes and quality of life (QOL) for the stroke patients due to earlier identification of the stroke and earlier treatment. The better outcomes among patients transported by the MSU might save costs for the healthcare payers due to lower post-stroke utilization of healthcare services (although this cost-saving could be partly offset by lower death rates in the MSU group). Nevertheless, any cost savings associated with post-stroke utilization have to be considered in combination with the high fixed costs of introducing and operating an MSU.

Evaluation of the MSU intervention is unique compared to most other interventions and medical therapies, because introducing and operating the MSU entails significant capital investment in outfitting an ambulance with a CT scanner and TM capabilities. In addition the MSU also requires provider/hospital level staffing changes predominantly in the form of hiring a VN to support the TM requirements of the MSU, and staff training to support MSU operations. These significant fixed costs imply that the agency operating the MSU requires additional reimbursement to compensate for these costs in order to ensure the financial viability and sustainability of the MSU operation. The providers supporting the TM management should also be reimbursed for their services. Hence an exploration of costs, aimed to provide an economic justification for higher reimbursements from the healthcare payers for an MSU dispatch, is a critical component of the intervention evaluation in this trial.

3. Preliminary Data

a. Steps in establishing the MSU

In order to address these gaps, we have introduced at the Texas Medical Center in Houston the nation's first MSU funded by donations from Dr Grotta's grateful patients, local philanthropists and the Frazer ambulance company. Not only are we the first center in the U.S. to put into operation an MSU, but we are the first (and only) group to employ it for clinical research purposes.

Fig 2 a, b: MSU exterior and interior

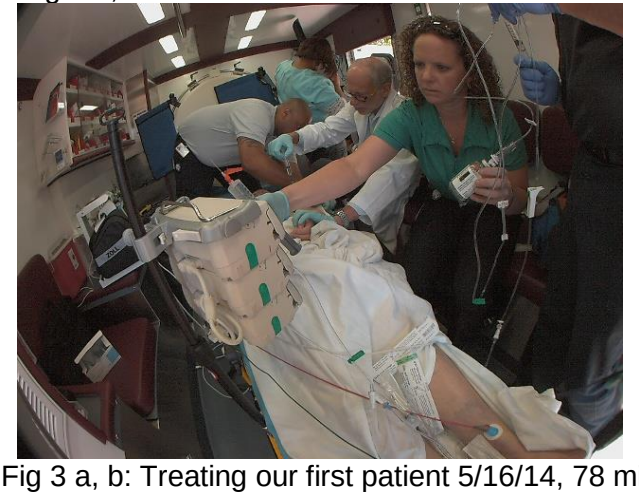


Fig 3 a, b: Treating our first patient 5/16/14, 78 min after symptom onset, with simultaneous TM backup

Conceptualization, Funding, and Build-out of the Houston MSU. The Houston MSU project was initially formulated after Dr. Grotta visited Drs Fassbender and Walter and then subsequently Dr Audebert in Berlin in 2012. Since there was no established pathway to implement a MS in the U.S., the following steps were begun more or less chronologically in March 2013.

- $1.8M was raised mainly from grateful patients, community philanthropists, and industry partners.
- Frazer Limited donated the ambulance "box" to UTHealth. Frazer Limited is located in Bellaire Texas, about 5 miles from the TMC.
- The CT scanner was purchased from Neurologica. Some equipment (cardiac monitor) and supplies were donated by Memorial Hermann Hospital (MHH), but most (ambulance chassis, stretcher, pumps, drugs, remaining supplies) were purchased from funds raised.
- The MSU was constructed at the Frazer factory—see links: http://www.frazerbilt.com/Videos/watch.php?id=784 https://www.youtube.com/watch?v=y1m64EL-k5I&index=6&list=UU7MwkvzzoUJ1SOHHl-PvLBQ
- Dr Grotta resigned his position as Chairman of the Department of Neurology to direct this project, form a consortium of local stakeholders, and apply for funding to enable completion of the study. Dr Grotta became employed by MHH and was provided 80% time to oversee operation of the MSU and the coordination of this clinical trial, as well as liability insurance covering his activity on the MSU.
- David Persse MD, medical director of the Houston Fire Department Emergency Medical Services (HFD EMS) was enlisted as a collaborator.
- The MSU staff-Project Manager (Stephanie Parker RN), CT technician, and 5 licensed Paramedics, along with part time VNs and RNs, was hired and on-call schedule developed.

- The MSU team became housed on the 14th floor of the UTHealth Professional Building (UTPB) located within 1 city block of all 3 CSCs, and the MSU parked in a dedicated spot in the driveway of this building with routing of appropriate power supply.

Licensing, Insurance, Contractual arrangements, and Institutional review

- The MSU was leased from UTHealth by MHH and licensed under a Texas state private ambulance provider's license held by MHH and its Life Flight helicopter ambulance service. MHH covers the insurance for MSU operations in case of accidental injury to patients or personnel. Patients carried by MSU are registered within the MHH system.
- The MSU passed both state and city ambulance inspection.
- A Clinical Trial agreement between UTHealth, MHH and the City of Houston and an exception to a city ordinance was signed by the mayor allowing transfer of patients from the city's EMS to the MSU.
- All physicians, nurses, paramedics and radiology technicians staffing the MSU hold appropriate Texas state practitioners licenses, passed Advanced Cardiac Life Support training, and have liability insurance.
- The MSU study protocol was approved by the Committee for the Protection of Human Subjects (CPHS) at UTHealth (HSC – MS- 13- 0322).
- We were informed by the FDA that an IND is not required for the MSU study (See Appendix 6).

Collaborations with regional stroke centers.

- The directors of the CSC Stroke Programs at St Lukes and Methodist Hospitals, and at the VA Hospital (Drs Suarez, Chiu, and Kent) agreed to collaborate and actively participate in the MSU study.
- The stroke teams and EDs at the destination CSCs agreed to adhere to the protocols to select patients for tPA and IAT treatment.

Collaboration and training of EMS

- The MSU is operated in collaboration with 3 EMS organizations; HFD EMS as well as EMS from West University Place and Bellaire, two subdivisions within Houston that are adjacent to the TMC.
- The MSU team met with and in-serviced the dispatch centers and paramedics from these EMS organizations, and a communication system was established.

b. PURSUIT Study (T.Wu P.I.)**.**

In the PURSUIT (Pre-hospital Utility of Rapid Stroke evaluation Using In-ambulance Telemedicine) study, we explored the feasibility and reliability of using TM in the ambulance to help evaluate acute stroke patients. Trained actors portrayed ten unique stroke scenarios, each conducted four times, and were retrieved and transported by HFD-EMS to our stroke center. A remote VN, based at UTHealth performed remote assessments in real-time and obtained clinical data points and NIHSS using the In-Touch RP-Xpress device. In 34/40 (85%) scenarios, the teleconsultation was conducted without major technical complication. The absolute agreement for intra-class-correlation (ICC) was 0.997 (95% CI: 0.992-0.999) for the NIHSS obtained during the real-time sessions. Matching of real-time assessments occurred for 88% (30/34) of NIHSS scores by ±2 points, and 96% of the clinical information[19].

c. Run-in phase

The Houston MSU went into service in May 2014. We planned a "run-in" phase to perfect our various alert mechanisms from EMS dispatch and on-scene EMTs, practice our on-scene interaction between the MSU team and the EMS squad including rendezvous, practice tPA administration and other patient management issues on board the MSU, get a preliminary evaluation of TM reliability, and rehearse our SM week interaction with EMS. The run-in phase included 9 MSU weeks and 2 SM weeks. During the MSU weeks, we were alerted 90 times, and enrolled and transported 25 patients. Reasons for non-enrollment mainly included time/wake up, hypoglycemia, syncope, TIA, seizure, migraine, and "other". During the run-in phase, we treated 13 patients with tPA on the MSU, and another patient met criteria for tPA treatment during the two SM weeks. Of the 13 tPA treated MSU patients, 31% were treated between 0-60 minutes from LSN, 38% between 61-90 minutes, 15% between 91-180 min, and 15% between 181-270 min. Of the 12 patients who were transported but not treated, the reasons for non-treatment were: 4 ICH, 3 seizures, 1 LSN >4.5 hrs, 1 SDH, 1 mimic, 2 TIA. Our average "on-scene" time for MSU transports was 28 min (range 12-53 min), with average alarm to treatment interval of 52

min (range 37-156 min). The one SM tPA eligible patient was treated in the ED during the 61-90 min interval from LSN. Of note, 4 of the 13 tPA treated patients on the MSU had baseline mRS > 2. Seven of the 12 pts with 90 day outcome data (one patient lost to f/u) had f/u mRS $\leq$ 1 point higher than baseline mRS. Ten TM consultations were attempted during MSU weeks, and all were completed. There were no TM technical issues, except on one occasion, the TM signal was intermittent due to inclement weather. Agreement between the MSU VN and TM VN on whether or not to administer tPA was 89%. Since the CT scanner came on-line, there have been no technical issues with CT scanning or CT scanner performance.

d. Initiation of randomization and progress to date

After this run-in phase, we began randomized MSU and SM weeks on August 18, 2014. We remain blinded to data on MSU vs SM weeks since randomization began. During the first 14 MSU + 13 SM weeks, we have enrolled a total of 74 patients, and treated 45 with tPA. For planning our ability to recruit our required sample size of tPA treated patients, this equates to approximately 1.7 tPA treated patients per week overall. There have been zero TM or CT technical concerns since randomization began. We have been able to obtain informed consent in all enrolled patients, and obtain 90 day f/u in 90% of enrolled patients who have survived to 90 days. N.B. Once the MSU is deployed, we cannot pre-screen patients before enrollment for likelihood of follow up availability or for pre-stroke morbidity. Therefore, we have built a 10% lost to follow-up proportion into our sample size estimates, and assume based on our run-in data that about one third will have baseline mRS >2.

4. Study Design

We aim to carry out a prospective cohort study with randomized MSU or SM deployment weeks and blinded assessment of both trial entry as well as clinical outcomes. Since tPA treatment will occur at different time points in the study arms, our protocol is designed to reduce the potential for bias due to lack of allocation concealment. All potential stroke patients will be identified by a 911 dispatch center adhering to current standard of care protocols and subsequently screened for trial inclusion (confirmed neurological deficits with onset well within the IV-tPA treatment window and typical stroke mimics such as hypoglycemia excluded) at the same pre-hospital time by the same investigators on both MSU and SM weeks to ensure that comparisons are made between similar patients. Anyone transported on the MSU (or deemed eligible for MSU transport on SM weeks) will be considered as enrolled into the study and eventually consented for participation. Therefore, comparable patients in the SM group will also be enrolled and consented. For all patients enrolled, criteria for study enrollment and tPA treatment will be subsequently reviewed by a vascular neurologist blinded to MSU vs SM assignment. For comparing outcomes between MSU and SM, we will only include patients meeting criteria for tPA treatment on the MSU, or similar patients on SM weeks, whether or not actually treated, based on a blinded review of prehospital information. We will report baseline comparability of clusters (patient co-morbidities, age, and stroke severity), plan an intention-to-treat analysis, and will implement an aggressive protocol to reduce lost to follow-up and thus differential missing data. Finally, all 3 month mRS measurements will utilize a standardized questionnaire (Rankin Focused Assessment) which will be obtained from the patient by an investigator blinded to treatment allocation.

5. Inclusion Criteria

There will be three decision points for inclusion of patients into either the MSU or SM arms (**see flow chart, Appendix 1**): 1. Whether to call the MSU team at the time of the 911 call or EMT evaluation; 2. Whether the patient might be a tPA candidate when evaluated by the MSU team pre-hospital; 3. Whether the patient meets criteria for IV tPA treatment.

1. **Criteria to alert MSU Team (by either a, b, c, or d, and meeting all criteria i-iv):**
    - **a.** HFD, Bellaire or West University EMS dispatch center based on caller identification of possible stroke
    - **b.** EMT or paramedic on scene recognizing a possible stroke
    - **c.** MSU team identifies a possible stroke by monitoring EMS communications

d. EMS base station calls MSU team for stroke patient en-route to one of the CSCs

i. Last seen normal on the same day as 911 call to EMS dispatch, and after awakening

ii. EMS decision to transport the patient to one of the CSCs within pre-designated "catchment area" of MSU

iii. Call to dispatch within pre-established hours of availability

iv. ≥ 18 years old

2. Criteria for MSU team to enroll patient into study (to be carried out pre-hospital)

i. Last seen normal (LSN) possibly within 4hr 30 min

ii. History and physical/neurological examination consistent with acute stroke

iii. No definite tPA exclusions per guidelines[1], prior to CT scan or baseline labs

iv. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment, including IV tPA, will not be delayed for consent; however, consent in both MSU and SM patients must eventually be obtained for data to be retained for analysis.

3. **Criteria for tPA eligibility** (to be determined pre-hospital on MSU weeks and after ED assessment on SM weeks, and confirmed by blinded adjudication

i. Meeting ard tPA inclusion and exclusion criteria per guidelines[1] after CT scan, baseline labs, and clinical re-evaluation

6. Study Population

To be assessed for eligibility	(n = 5000)
To be enrolled	(n = 1100)
To be analyzed ("tPA eligible")	(n =541)

Based on our pilot data in the first 9 months of operation, the MSU is being alerted and dispatched by Criteria 1 above approximately 5 times for every patient that is enrolled into the study by Criteria 2, and 10 times for every patient treated with tPA by Criteria 3. Therefore, we anticipate that slightly over 50% of enrolled patients will be treated with tPA. We calculate that we will need 541 tPA eligible patients (meeting above Criteria 1, 2 and 3) to answer SA 1 allowing for 10% lost to f/u, 162 enrolled patients (meeting Criteria 1 and 2) to answer SAs 2, and 96-740 tPA eligible patients to answer SA 3 (see Statistical Methods).

7. Intervention- detailed description of the current process of conducting the study.

Prehospital stroke treatment with the MSU (diagnostic procedures and possible stroke treatment in the MSU) will be compared with standard management (SM -- patient transported via EMS to a CSC). The intervention has been designed to ensure maximal speed of response, capture as many stroke patients as possible, and unbiased enrollment of similar patients into both comparison groups.

7a. Integration of the trial into routine emergency medical service (EMS): All emergency 911 calls are routed automatically to the Houston, Bellaire, or West University EMS dispatch centers. Enrollment into this study takes place from 7 am to 11 pm, 7 days/ week. At 7 am and 11 pm, the MSU team calls the EMS dispatch centers and places the MSU team on or off call. During on-call hours, the EMS dispatch centers alert the MSU team via dedicated pager and cell phone for all possible stroke patients (see below), but the MSU is only dispatched on 50% of the weeks. On non-MSU dispatch weeks (SM weeks), the MSU team is still dispatched but travels in a private vehicle (N.B. Neither the UT CPHS or EMS will allow us to arrive on-site with the MSU and not utilize it if the patient is having a stroke. Therefore, we cannot dispatch the MSU to the scene on SM weeks, and furthermore, we cannot exclude patients who qualify for tPA treatment on the basis of uncertainty of follow-up or pre-stroke disablility).

7b. Notification of the MSU team. Once the MSU team notifies the dispatch center that they are on-call, 911 calls are screened for stroke symptoms by EMS dispatchers. Both the dispatchers and their supervisors have been trained in stroke symptoms by the MSU Team. Training includes an instructional DVD reviewing stroke symptoms and loaded onto their computers, and a printed algorithm of questions to be asked if stroke is suspected. Currently, all calls are immediately triaged by the dispatcher onto one of 44 diagnostic pathways such as "fall", "chest pain", "gunshot", etc. Only one of these pathways is "stroke". After listening to the initial history, the dispatcher immediately dispatches the nearest available Emergency Medical Technician (EMT) or Paramedic team depending on proximity of available units and severity level of the pathway. After EMT/paramedic dispatch, the MSU team is activated by one of four pathways (see Criteria 1, in Section 4 above). 1). If the caller mentions the word "stroke", the call is triaged onto the "stroke" pathway and if the patients is within the 5 mile catchment area of the MSU (see below), the dispatcher also immediately dispatches the MSU team using a dedicated beeper and cell phone line. 2). If the patient is triaged on one of the non-stroke pathways and the MSU team is not alerted by the dispatch center, but the EMT or paramedic arrives on the scene, discovers that the patient may have had a stroke, and that one of the designated CSCs is a possible transport option, they call back to the dispatch center and ask for MSU team dispatch. All EMTs and paramedics operating within the catchment area of the MSU have been trained in stroke recognition and the need to ask for MSU team dispatch. 3). The MSU team monitors all communication between dispatch and EMS units, and if a possible stroke patient is identified, the MSU team contacts the EMS unit and ask to be "added on" to the call if one of the designated CSCs is a possible transport option. 4). All EMS units transporting stroke patients call the base station for instructions and hospital pre-notification. The base station alerts the MSU team for all transported stroke patients. This serves as a "back up" to methods 1-3. If the MSU team is notified by any of these 4 pathways for a possible stroke and the patient meets Inclusion Criteria as in section 4.1.b.i-iv, the MSU team is deployed. Either the MSU is dispatched, or the SM pathway, which already has been initiated, is continued.

7c. Mobile Stroke Unit process: The MSU is staffed by an off-duty Houston Fire Department paramedic, certified CT technician, Vascular Neurologist (VN faculty or fellow) and research nurse (RN). The MSU team alerts the on-call TM VN who immediately connects from the central TM office at UT Medical School to the mobile TM device on the MSU. Once alerted, the MSU is driven by the paramedic with the VN riding "shotgun" and helping to navigate, while the CT tech and RN ride in the back.

The MSU is stationed in the driveway of the UT-Professional Building (UTPB) which houses the MSU team offices on the 14th floor. There is an elevator outside the MSU team office door leading to the outside door opening onto the designated MSU parking spot. The UTPB is in the heart of the Texas Medical Center (TMC), and surrounded by the 3 CSCs which are the destination of all MSU transports. Currently, direct dispatches of the MSU by EMS are limited to a 5 mile radius of the MSU office. We have found that the 5 mile radius "catchment area" allows dispatch and arrival of the MSU at the emergency site during the time EMS is still on-scene evaluating the patient. This catchment area will become expanded needed (see Recruitment Plan). Additionally, the MSU is alerted to patients from outside the catchment area by pathways # 2 or 3 in section 6b. Under any of these pathways, if the MSU cannot reach the patient before the EMS unit is ready to depart the scene with the patient, the MSU can arrange to "rendezvous" with the EMS squad en-route. Both the paramedic and RN carry a two-way HFD radio and establish direct radio communication with the EMS team in charge of the patient on site. This enables the MSU team to notify the on-site EMS team that they are en-route, their ETA, and, in some cases, the need to rendezvous. Also, the two way radio allows the on-site EMS squad to "disregard" the MSU if the squad determines that the patient does not have a qualifying stroke.

Once on scene, the patient's medical history, vital signs, finger stick glucose, and physical examination are jointly evaluated by the EMS paramedics and MSU VN and RN, and if the patient has signs and symptoms of stroke possibly within 4 hours 30 min of LSN they are moved into the MSU. This is a critical decision point (see Criteria 2, in Section 4 above). **If the patient meets all inclusion criteria except lab and CT (which have not yet been done), the patient is then <u>enrolled</u> into the study for**

purposes of answering the Specific Aims, and assigned to the MSU arm. If the patient does not have signs and symptoms of a stroke, is clearly outside the 4.5 hour time window, has other definite tPA exclusions, or is clinically unstable (such as requiring pressor or ventilator support), they are managed and transported per EMS routine. These patients are considered "screen failures" and a one page CRF completed including diagnosis and reason for exclusion.

Making the tPA decision and the relative roles of the TM VN and on-site VN and MSU team. The following interaction is how we have developed the workflow in order to avoid delay while at the same time allowing the TM VN and on-site VN to make totally independent decisions about tPA treatment without ever knowing the others' decision. The initial evaluation of the patient and decision whether or not to enroll the patient is made off the MSU in the patient's home, workplace etc, or in the case of a rendezvous, in the adjacent HFD ambulance, by the on-site VN. During this time, the on-site VN obtains the initial history, exam and NIHSS. Once the on-site VN decides to enroll the patient, the patient is moved into the MSU, and vital signs measured, IV access obtained, and blood samples analyzed via a point of care (POC) laboratory (blood glucose, hematocrit, INR if needed) by the RN. The on-site VN works with the RN to control blood pressure, oxygenation, glucose etc as needed. Simultaneous to these events once the patient is moved into the MSU, the TM VN evaluates the patient with the help of the paramedic, using the portable In-Touch RP-Xpress mounted at the foot of the patient's gurney or hand held by the paramedic to optimize viewing. The paramedic (and RN if necessary) communicates with the TM VN over the TM device helping the TM VN obtain the history and carry out the NIHSS, and record the vital signs and POC lab results. During the TM VN evaluation, the CT tech is positioning the patient for the CT scan. Once the RN has the IV in place, labs completed, and VS stable, and the CT tech has the patient in position, the TM consult is interrupted and a non-contrast CT scan of the head performed. The CT technician immediately uploads the data onto PACS for immediate visualization on the MSU laptop computer, and also securely and wirelessly sends it via on-board 4G connection in real time to a secure PACS system for review by the TM VN. Eventually the images are also pushed via a dicom grid to the receiving facility. While the on-site VN is reading the CT scan on the laptop (located outside the MSU so the on-site VN does not observe the remainder of the TM consult), the TM VN completes their evaluation with the assistance of the RN, and signs off, ending the TM consult. The on-site VN, after completing their review of the CT scan, and after the remote TM VN has signed off, completes their evaluation including NIHSS, and decides whether the patient qualifies for tPA ("**therapy decision time**"). If the patient meets all inclusion and exclusion criteria for thrombolysis according to published guidelines, the IV tPA bolus is given without delay **("tPA needle time")**, followed by the infusion. If after seeing the labs, CT scan, vital signs and neurological exam, the on-site VN thinks that the patient does not qualify, tPA is deferred. The ultimate decision whether or not to give tPA is made by the on-site VN, without knowledge of the TM VN decision.

After tPA is initiated, or the decision made to withhold tPA, the patient is then transported in the MSU with RN and VN to the appropriate CSC (the paramedic drives with the CT tech riding in the front). Patients receive standard EMS routine pre-hospital stroke care en-route, and if treated with tPA also receive standard post-tPA monitoring (q15 min VS, neuro checks and observation for angioedema). Destination hospitals include any of the certified CSCs within the 5 mile radius catchment area of the TMC, and are selected by EMS according to their usual criteria. The destination hospital and their stroke team are pre-notified by the MSU team, and all further care carried out at the destination ED according to their usual routine. The RN or VN obtain consent, and visit the patient on days 0-3 at the hospital and day 90 in clinic or at home, and record study related data on the CRF.

If the MSU is called during the "on-call" period for a potential patient, but cannot reach the emergency site before EMS is likely to reach the destination hospital (because the MSU is otherwise occupied on a simultaneous call, traffic, the emergency site is too far away, or equipment malfunction), the patient is not included in the study, but the reason for the "missed" patient is recorded.

7d. Standard management: The MSU is not dispatched, but the MSU RN or VN is dispatched by car to the scene or meets the patient and EMS squad at the destination ED. The destination CSC is determined by EMS (these are the same complement of hospitals served by the MSU) and the hospital

stroke team is pre-notified by EMS. Once on scene or at the ED, the patient's history, time last seen normal, vital signs, finger stick glucose, and physical examination are obtained from the EMS paramedics by the MSU VN or RN who then carry out their own NIHSS without delaying the EMS evaluation, transport or ED intake process, **If the patient meets all inclusion criteria except lab and CT (which have not yet been done), the patient is then enrolled into the study for purposes of answering the Specific Aims, and assigned to the SM arm**. If the patient does not have signs and symptoms of a stroke, is clearly outside the 4.5 hour time window, has other definite tPA exclusions, or is clinically unstable (such as requiring pressor or ventilator support), they are not enrolled and are managed per EMS and ED routine. These patients are considered "screen failures" and a one page CRF completed including diagnosis and reason for exclusion. Following the decision to enroll the patient, the MSU VN or RN then decide if the patient meets criteria for tPA. **If the patient meets all inclusion and exclusion criteria for thrombolysis according to published guidelines during the pre-hospital evaluation by EMS and the MSU team, and if the baseline labs and CT scan obtained once the patient reaches the ED do not exclude the patient, then the patient is considered a "SM tPA treated patient"**, whether or not they eventually receive tPA in the ED (for instance, the 4.5 hour time window might be exceeded, or the patient's deficit might have resolved, by the time the patient is fully evaluated in the ED).

The hospital based stroke team manages the patient as per stroke center routine and the same standard of care analyses carried out as with the MSU treatment. IV tPA is given as per the hospital based stroke team. If the patient does receive tPA in the ED, the "**therapy decision time**", and **"tPA needle time"** are recorded. For all SM enrolled patients, whether or not they actually receive tPA, the RN or VN obtain consent, and visit the patient on days 0-3 at the hospital and day 90 in clinic or at home, and record study related data on the CRF.

TM is not carried out on SM weeks.

Blinded adjudication: All enrolled patients are reviewed by a VN blinded to assignment of MSU vs SM management and not involved with either MSU or remote TM patient management. The blinded VN determines from a dedicated "adjudication form" that is missing any time data or other information that would produce unblinding, if the patient meets criteria for study enrollment and for tPA treatment. If the patient is enrolled or treated with tPA (or on SM weeks deemed to be a "SM tPA treated patient") but do not meet criteria, they will not be included in data analysis comparing MSU to SM weeks. If an enrolled patient meets criteria for tPA but is not treated, pre-hospital, that fact will be noted and the patient considered a "miss".

BP: On both MSU and SM weeks, blood pressure is measured at baseline and thereafter according to EMS routine, and treated to target levels, according to published guidelines for ischemic stroke, pre and post-tPA treatment, and for intracerebral hemorrhage. The time of first BP treatment is recorded.

CT: A cerebral CT scan must be performed on all patients meeting Inclusion Criteria for IV tPA, and the CT scan must be read by the MSU VN prior to the initiation of tPA treatment. All CT scans are officially interpreted later by the radiologist at the destination hospital. Follow up CT or MRI imaging is optional as is the timing. It is carried out as per routine care and results recorded if done. CT or MRI are immediately performed in the case of neurological deterioration.

TM: We use existing portable telemedicine units available from In Touch Health (Santa Barbara, CA; http://www.intouchhealth.com). The RPXpress System is a mobile, robotic communications platform that allows physicians bidirectional communication over remote distances via the Internet comprised of audio and video using a 175° field of view fisheye camera capable of 6× zoom and a high-quality hypercardioid microphone and full-range speaker integrated into the portable device. The device is Food and Drug Administration–approved for patient monitoring and connection to diagnostic medical devices. The established connection is Health Insurance Portability and Accountability Act (HIPAA) compliant and encrypted. VNs connect to the device from a desktop computer located at the University of Texas at Houston Medical School Building. Connections are encrypted using a combination of RSA

public/private key and 256-bit advanced encryption standard symmetrical encryption to ensure confidentiality of patient information transmitted.

8. Informed consent (**Appendix 2**)

Informed consent is obtained at any time during this process by the MSU VN or RN from either the patient (if competent) or legal representative. In no case is standard of care, including CT scanning and tPA administration whether in the MSU or hospital, delayed in order to get informed consent. This study only involves standard of care management of stroke patients according to current guidelines, and patients are managed in the MSU by personnel with the same training and expertise as they would receive in the CSC stroke center ED, and costs to the patient for their pre-hospital and ED care are the same whether they are managed on the MSU or SM pathway. **According to current HFD EMS policy, all acute stroke patients within the 5 mile catchment area of the MSU are transported to the same CSCs that receive MSU patients so that the study does not involve "re-routing" of patients**. Specifically regarding costs, patients are charged the same technical fee for CT scanning, tPA and other medications whether administered in the MSU or ED, and pre-hospital transport is billed the same whether by MSU or SM. The CT reading professional fee is also the same whether the CT is carried out in the MSU or ED. Regarding risks, there is no evidence that a CT scan and other diagnostic procedures performed in the same way as in the hospital, but at the site where the patient is found, is less effective or has more complications than in a hospital. A CT scan is performed whether the patient is in the study or not to determine diagnosis of a stroke. The CT scan exposes patients to a small amount of radiation, (about 1.02 cGY). Since CT scanning, tPA administration, and all other pre-hospital procedures in this protocol **including choice of destination hospital** are standard of care and follow published guidelines, The UT Committee for the Protection of Human Subjects has ruled that informed consent is not required prior to their performance. Informed consent is needed to include patient data for this study. Consent is usually not obtained until the standard of care acute stroke patient care process is complete and the patient and/or legal authorized representative has adequate opportunity to review the informed consent document. Data recorded by the research nurse will be discarded if consent is not obtained. If the patient refuses to participate, this will not have any influence on either diagnostic or therapeutic procedures. We have considered exception from informed consent, but a very low percentage of our patients have both decreased consciousness/inability to communicate or no legal relative. To date, we have been able to obtain consent on 100% of our enrolled patients.

9. Concomitant therapy

All treatments are given according to standard of care protocols or published guidelines. Off-protocol unapproved treatments are not allowed. The use of intra-arterial thrombectomy (IAT) is allowed in this study but is limited by the same strict protocol at all hospitals to patients with carotid T, M1, A1, proximal M2, or basilar occlusions on screening vascular studies, and groin puncture within 6 hours (4 hours prior to 2/16/15) of symptom onset (see Appendix 3). To date, about 17% of MSU tPA treated patients have received IAT. Although this number is relatively small, we recognize the possibility of "collider bias" in interpreting MSU vs SM results in the subgroup of patients undergoing IAT (see Potential Biases section 13). Conceivably, MSU pts will need less IAT if they respond to earlier tPA, or, if they need IAT, MSU pts may get it faster due to earlier warning, so that better outcomes in those patients may be due to earlier IAT and not directly due to earlier tPA treatment. Also, benefit from IAT in SM patients may obscure the positive effect of the MSU intervention. While these considerations may confound interpretation of the results, they should not prevent us from determining if MSU has a beneficial effect if added to background therapy. Considering that IAT is now considered background therapy, the main impact of IAT will be on the expected 90 day mRS and therefore the power/sample size. A sensitivity analysis will be carried out both including and excluding patients receiving IAT.

10. Recruitment and Retention Plan

Although we plan to carry out this study with only one MSU, we calculate that we will be able to recruit enough patients to answer the Specific Aims. We have already implemented our first recruitment stimulus by arranging, through 2-way radio contact between the MSU and EMS units in the field, to rendezvous with EMS units bringing stroke patients to the TMC from beyond our 5 mile (radius) catchment area. **Transport of some patients to the CSCs in this study from beyond 5 miles and paramedic rendezvous are already part of routine EMS practice and does not involve „re-**

routing“ of patients for this study. If the dispatched EMS crew identifies a stroke patient who would benefit from CSC care at the TMC based on either it being a more severe stroke or because of non-availability of a Primary Stroke Center, recently amended EMS policy allows paramedics to deliver the patient directly to the CSC EDs in the TMC. The EMS unit transporting the patient calls the dispatch center and tells them they are bringing a patient to the TMC and to dispatch the MSU. Once dispatched, the MSU establishes direct radio contact with the EMS unit, confirms inclusion and exclusion criteria as much as possible, and arranges for a rendezvous site where the patient is quickly evaluated by the MSU team and then moved into the MSU. Subsequent management is exactly as previously described for patients within the catchment area. Our preliminary data support our ability to recruit sufficient patients. During the first 27 weeks of MSU operations (14 MSU weeks and 13 SM weeks), 45 patients have been treated with tPA on the MSU or would have been treated during the SM weeks, which prorates to over 80 tPA treated patients per year (see pilot data).

Another strategy to increase enrollment is to identify a second location for the MSU in a neighborhood with high stroke incidence. The MSU „on“ and „off“ weeks at this second location would complement the „off“ and „on“ weeks of the unit when it is located at the TMC so that the MSU will constantly be „on“ and enrolling patients, either at the TMC or the second site. This proposal has already been approved by Dr Persse, Medical Director of HFD-EMS. The main obstacle to implementing this strategy is raising additional funds to pay the salaries of the VN, nurse, CT tech and paramedics who will man the MSU at the second location. Dr Grotta is currently approaching potential donors to raise the money to support these personnel. We have already identified the best second location (at Memorial Hermann Hospital Southwest), a large primary stroke center „in pursuit“ of CSC designation, and located in an area with very high stroke density largely populated by Hispanic and Asian individuals.

While we believe the measures we have implemented will result in successful timely completion of this study, we recognize that the key to successful recruitment rests with the enthusiasm of EMS to help with this study. To date, the MSU team has made 40 visits to HFD Fire Stations to meet individually with the EMTs and Paramedics who will be alerting us to patients with stroke and working with us in the pre-hospital environment. In addition, we have in-serviced 696 dispatchers and their supervisors. To maintain enthusiasm, we have instituted an EMT/paramedic recognition program that sends electronic (per twitter or other social media) messages recognizing the EMS units that alert us to a patient we enroll. Such positive feedback to EMS was very successful during the NINDS tPA Stroke Study and paramedics often stop us to proudly remind us of certificates of recognition they received years ago.

We maintain an aggressive program to prevent patients lost-to-follow up. Since the intervention our team is conducting in this trial requires our leaving the medical center to treat patients all over the city, doing the same to obtain 3 month follow up in the case the patient cannot return to the medical center has not been a problem or a break from routine operations in this study. To date, of all tPA treated patients during our run-in phase and randomization who have survived to 90 days to date, we have obtained outcome data on over 90%. Because we cannot pre-screen out patients unlikely to follow-up, we have built a 10% lost to follow-up rate into our sample size calculations.

Finally, we have been working with Dr Andrei Alexandrov at the University of Tennessee in Memphis, and Dr William Jones at the University of Colorado in Denver to establish their own MSU programs. Local funding has been obtained to purchase and equip an MSU at both places and they should be operational within 1 year. Dr Grotta has made two site visits to each location, and both have agreed to participate and enroll patients into the BEST-MSU study (see letters of agreement). Once these programs are up and running, supplemental funding may be requested to provide the additional research support needed to do this work and to transmit data to our data coordinating center. It is impossible to know at this point how many additional patients could be enrolled during the 5 years of this grant if those centers are added. However, both centers have very active acute stroke treatment programs and collaborative EMS directors. The additional patients would enable us additional power to answer our Specific Aims, and would also increase the generalizability of our results.

11. <u>Outcomes for Specific Aims</u>

Outcomes for S.A. 1 (in hierarchical sequence of importance).

1. Change in Utility-weighted mRS from baseline tot 90 days, comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks. **Primary outcome**.

2.

    a. Change in utility-weighted mRS from baseline to 90 days,

    b. ordinal (shift) analysis of mRS at 90 days, and

    c. proportion of patients achieving 90 day mRS 0,1 vs 2-6

of enrolled patients treated with tPA within 60 minutes of LSN onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS) between the groups at the time of treatment. **N.B**. Patients will include only those patients actually treated with tPA based on the final determination of the time LSN, and will include only patients meeting all inclusion and exclusion criteria.

3.

    a. ordinal (shift) analysis of mRS at 90 days, and

    b. proportion of patients achieving 90 day mRS 0,1 vs 2-6

comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks.

4. The time from LSN to tPA treatment on all patients treated within 4.5 hours of LSN on MSU weeks compared to similarly eligible patients on SM weeks. **N.B**. Patients will include all enrolled patients actually treated with tPA (or on SM weeks, eligible for tPA treatment) meeting all inclusion and exclusion criteria, and based on the final determination of time of LSN. One analysis will compare the median times. A second analysis will also capture the patients who were eligible but did not receive tPA because it was too late, categorizing time into the following groups (e.g., 0-60min, 61-90min, 91min-180min, 181-270min, eligible but no tmt because>270).

5. Of the enrolled patients that were eligible for treatment with tPA (according to published guidelines) on MSU weeks compared to SM weeks, the percent that were treated within 4.5 hours and within 60 minutes of LSN.

6. The time from LSN and from ED arrival to start of endovascular procedure (intra-arterial thrombectomy-IAT) in patients who meet pre-specified criteria for IAT on MSU weeks compared to SM weeks. **N.B.** All patients receiving IAT will be included in this outcome.

7. The median/mean time from LSN to tPA therapy decision on all patients considered for treatment within 4.5 hours of LSN on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patients meeting inclusion criteria whether or not treated with tPA.

8. Time between 911 call and onset of etiology-specific BP management on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patients.

Safety Outcomes for S.A. 1

1. The incidence of symptomatic intracranial hemorrhage (sICH) in enrolled tPA treated patients on MSU weeks compared to SM weeks (Symptomatic intracranial hemorrhage defined as any intracranial blood accumulation associated with a clinical deterioration of $\geq$ 4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration) **N.B.** Patients will include all patients treated with tPA, whether or not they meet all inclusion and exclusion criteria.

2. Mortality. **N.B.** All enrolled patients signing informed consent will be included in this endpoint and followed until 1 year.

3. The incidence of stroke mimics and transient ischemic attacks (TIAs) in tPA treated patients on MSU weeks compared to SM weeks. **N.B**. SM patients deemed eligible for tPA on their pre-hospital assessment who then completely recover by the time of arrival in the ED will equal the excess incidence of TIAs treated on the MSU pathway.

Outcomes for SA 2.

1. The agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU. **N.B**. Patients will include all enrolled patients on MSU weeks considered for tPA treatment. .
    a**.** Frequency and causes of incomplete or failed TM consultations.

Outcome for SA 3.

1. An exploratory cost-effectiveness analysis of MSU versus SM using the Incremental Cost Effectiveness Ratio and Incremental Net Benefit estimate will be performed. **N.B**. The exploratory cost-effectiveness analysis (CEA) will include all enrolled patients on MSU and SM weeks found eligible for tPA (based on blinded review of the patient's chart, regardless of whether they were treated or not)

12. Statistical Plan

Randomization

For this exploratory clinical trial we randomize the weeks of deployment of the MSU. A permuted blocked randomization scheme is used to assure balance over time in the intervention groups. Block sizes are randomly chosen to avoid revealing a treatment assignment based on the enrollment date.

Blinding

On MSU and SM deployment weeks there is a blinded assessment of the qualifications of patients for study enrollment and tPA treatment, as well as blinded assessment of clinical outcomes. Since the decision for enrollment and tPA treatment occurs at different time points in the study arms (see flow chart Appendix 1), our protocol is designed to reduce the potential for bias due to lack of allocation concealment. All patients are reviewed for their qualifications for both enrollment and tPA treatment by a VN blinded to MSU vs SM assignment, and only those meeting all qualification criteria will be included in group comparisons. This assessment occurs after acute patient management is completed, and carried out by a VN not involved with any on-site or TM patient management and is based on a CRF omitting any time information or data that would result in un-blinding. Finally, the primary outcome, 90 day mRS, is assessed by trained investigators blinded to treatment group using an objective rating device (Rankin Focused Assessment).

We also ensure that the on-site VN and TM VN make their assessments about tPA eligibility independently without knowledge of each other's decision (see Section 4, study design).

Data Collection

Direct data collection begins at time of screening and continues until it has been determined that the subject is not eligible for this trial, the patient or family refuses consent, the patient drops out of the study, or completes the study. Until deemed ineligible, data from subjects are collected and reviewed for screening purposes. Data on eligibility are submitted to the DCC to allow a description of screened versus enrolled subjects.

Figure 1 shows the type and timing of data collected.

Data are collected on all subjects who have consented to continue in the trial. Data are collected using standardized case report forms. After data collection, the data are entered into to a secure, web-based data system designed for this trial. The web-based program provides the flexibility of entering data from multiple locations and centralizes the data management process. To ensure security, each user is assigned a username and password and this username, date and time of each login is recorded in a login history file to ensure a record is maintained of each access to the system. This information is also recorded in the change history audit logs. The data entered for the BEST-MSU trial are maintained in a secure database at the DCC.

Selected elements from the medical records (radiology reports, OR notes, patient history, morbidity and mortality notes, etc.) are collected in a HIPPA compliant manner. For subjects discharged to another facility, the clinical research staff completes an authorization form to release protected health information (PHI) and obtain signatures from the subject or LAR prior to discharge.

12.a. Analysis Plan for Outcome S.A. 1: Compare outcome with MSU vs SM in tPA eligible patients

This study will determine if tPA eligible patients enrolled on randomized weeks when a MSU is available will have less disability at 90 days after stroke onset, compared to patients enrolled on weeks when MSU was not available.

Primary Outcome: A substantial number of stroke patients (roughly 33% in our preliminary data) who qualify for tPA treatment on the MSU have pre-existing disabilities making it impossible to achieve a favorable mRS outcome. Therefore, analyses of the primary outcome will include a utility-weighted mRS[29], allowing for patients who begin with disability of having a favorable outcome if they have some significant clinical improvement. The utility-weighted mRS assigns values to each mRS grade depending on patients' value of that level of function, with lower mRS scores (reflecting less disability) given proportionately higher weight than higher mRS scores (reflecting more disability). The primary outcome is the change in patient-centered utility-weighted mRS (Δ uw-mRS) from baseline to 90 days in patients found eligible for tPA on MSU weeks compared to SM weeks. The uw- mRS assigns values to each mRS grade depending on patients' value of that level of function, with lower mRS scores (reflecting less disability) given proportionately higher weight than higher mRS scores (reflecting more disability). The difference in the mean Δ uw-mRS between the MSU and SM groups will be estimated along with corresponding two-sided 95% confidence intervals. This patient centered endpoint is being utilized in the DAWN stroke trial (http://clinicaltrials.gov/ct2/show/study/NCT02142283).

Power/Sample Size Calculations: 80% power to detect a difference between groups of 0.1 in the mean Δ uw-mRS from baseline to 90d (the primary patient-centered outcome) using a two-sample t-test (see below for assumptions about s.d., and underlying event rate). 563 (total), 362 MSU, 201 SM + 10% lost to f/u (assuming 1.8 times as many patients will be recruited in MSU weeks than in SM weeks). See timeline for expected enrollment.

Hypothesized Effect Size for Intervention on Main Patient-Centered Outcome: In 90 patients randomized in our pilot study comparing a combination of Argatroban + tPA to standard tPA treatment, 90 d mean+s.d. Δ uw-mRS was 0.59+ 0.35 with the combination vs 0.49+ 0.37 with tPA alone, similar to the difference we project. In a re-analysis of 11 other acute stroke studies[29], the difference in mean 90d Δ uw-mRS between groups ranged from 0.024-0.25, with most trials in the range of 0.1. For instance, 90d Δ uw-mRS was 0.59 vs 0.50 with tPA vs placebo in the NINDS tPA trials.

Baseline Analyses. Although the random assignment of participants to the two treatment arms should ensure comparability with respect to known and unknown variables, imbalance may occur by chance. Descriptive statistics for baseline characteristics known or suspected to be associated with outcomes will be prepared for the two treatment groups for all randomized as well as all that were deemed „eligible for tPA“ based on the blinded review. Chi-square statistics and Wilcoxon rank sum tests will be used to evaluate the differences between the arms with reference to baseline characteristics between categorical and continuous variables, respectively. Any variables with observed baseline differences will be included in secondary adjusted analyses. Also, completers will be compared to non-completers (loss to follow-up for 90 mRS) on these baseline variables to indicate whether missingness may be considered random.

Interim Futility Analysis. An interim analysis for futility of the treatment group with respect to theprimary outcome will be conducted when one-half of the 90 day outcomes have been collected. The outcome will be monitored using a two-sided O'Brien-Fleming boundary with Lan-DeMets alpha spending function[30,31].

The futility analysis of the 90 day dichotomized mRS (0-1 vs 2-6) will be a 2-sample, 1-sided, test of proportions. The benefit of this futility analysis is the ability to compare the mRS, a patient-centered outcome, using a smaller sample size than in a traditional efficacy trial.

The futility analysis will compare patients in MSU weeks vs SM weeks ($\alpha = 0.15$). If we reject the null hypothesis that the percentage of favorable outcomes (mRS<2) in patients in the MSU weeks is greater than or equal to the percentage of favorable outcomes in patients in the SM weeks plus 10%, we conclude that completing the trial would likely be futile. The futility hypotheses are:

$H_0: p_{MSU} - p_{SM} \geq \Delta$

$H_A: p_{MSU} - p_{SM} < \Delta$

where p_{MSU} and p_{SM} are the proportions of participants expected to have a favorable mRS outcome in the MSU and SM groups, respectively, and Δ denotes the 10% increase in favorable outcomes over SM considered clinically meaningful.

Analysis of Primary Outcome. The mean change in this outcome from baseline to 90d will be compared between groups using a two-sample t-test. If the assumption of normality does not hold, we will conduct a Wilcoxon rank sum test.

Adjusted analyses. The analyses of mRS will be adjusted for any baseline covariates that were statistically significantly different among the two groups and covariates that are known to be associated with mRS, including baseline NIHSS, age, use of IAT, and previous TIA/stroke incidence.

Analyses of Secondary Outcomes.

A Wilcoxon rank sum test will be used to determine the differences between the two groups in median time to treatments and therapy decision. Categorical outcomes will be analyzed using Fisher's exact test.

A logistic regression model will be used to compare 90 day mRS 0,1 vs 2-6 of patients treated with tPA within 60 minutes of symptom onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS, use of IAT, and previous stroke/TIA incidence) between the groups at the time of treatment[33]. For a two-sided test, assuming that earlier treatment on the MSU will result in a higher probability of achieving an mRS of 0,1, assuming a 1:2 allocation (preliminary data show that 30-40% are treated within 60 min and 60-70% later), a sample size of 93 with 0-60 min and 186 with 61-270 min will achieve 80% power to detect an odds ratio in the group proportions of 1.90, assuming that the proportion in SM is assumed to be 0.3400 under the null hypothesis and 0.4669 under the alternative hypothesis. The projected 541 tPA-eligible patients should provide us with sufficient power to answer this question.

Time to event data (e.g., mortality, time to treatment, and time to endovascular procedure) will be analyzed using Cox proportional hazards models, adjusting for baseline covariates NIHSS, age, and previous TIA/stroke incidence We will compare hazard rates for mortality between treatment groups adjusting for baseline covariates (ex: age, gender, Baseline NIHSS, glucose). We will follow the approach below to test for and take crossing hazards into account if applicable. As an additional analysis, we will compare mortality in the two groups adjusting for the covariates listed above and any additional baseline covariates that are imbalanced between treatment groups. If there are too many covariates to include in the model we will use a prescreening approach, testing covariates at the 0.20 level and including those that meet the latter criteria for significance. The validity of Cox regression model relies heavily on the assumption of proportionality of hazards. There are certain types of non-proportionality that will not be detected by the tests of non-proportionality alone but that might become obvious when looking at the graphs. We will use both graphical methods[34] and statistical tests to check the proportional hazards assumption.

We first use the graphic methods for detecting violations of the proportional hazards assumption. The plot of survival curves are based on the Cox Model and Kaplan-Meier estimates for each subgroup decided by covariates. Clear departures of two estimates indicate evidence against the assumption of proportional hazards. Another plot to be used is the plot of difference of the log cumulative baseline hazards versus time. Under proportional hazards, this plot is constant over time and centered on the estimated log-hazard ratio. Any time trend of the difference will suggest the violation of the proportionality assumption. Note that both plots only inform us if baseline hazards are proportional or not, and do not give detailed information about the type of departure from the proportionality.

The plot of martingale residuals could be further applied to determine the functional form to be used for a given covariate to best explain its effect on survival through a Cox proportional hazards model. The best functional form could be a transformation of the covariates (Z), such as log Z, or it may be a discretized version of the covariate. Under this situation, the martingale residuals are useful for determining cut points for the covariates. For example, we assume that Z_1 is a single covariate of the covariate vector Z for which we are unsure of what functional form of Z_1 to use. Let $f(Z_1)$ be the best function of the covariate Z_1 to explain on survival. To find the form of the function f, we will fit the data based on Z and compute the martingale residuals. Then we plot these residuals against the values of Z_1. The smoothed-fitted curve then gives an indication of the best function. For example, if the plot is linear, no transformation of Z_1 is needed. If the plot is a piece-wise constant, then a discretized version of Z_1 is suggested.

To formally test the assumption of the proportional hazards for the treatment effect, we will generate a time treatment interaction and refit the model to include the time treatment interaction. If the effect of the time treatment interaction is significantly different from zero, then the proportionality assumption is violated, and we will include a time treatment interaction in the model and choose the appropriate non-parametric approach[35].

Unless there is sufficient power (predetermined before the analysis is begun) the approach to ancillary analysis will generally be the calculation of confidence limits on intervention group differences rather than formal tests of significance as the trial may not have high power to detect difference in all of these outcomes. However, these comparisons will add to the knowledge of the benefits and risks of the intervention.

Heterogeneity of Treatment Effects

Tests of effects within subgroups will be driven by clinical rationale. To reduce the potential for spurious results, we would test for a sub-group treatment interaction at a 0.2 critical level. Any subgroup analyses that are not pre-specified would be considered post hoc and reported as requiring confirmation in future studies. For pre-specified subgroups with significant treatment-by-subgroup interactions, estimates of the MSU effect will be obtained separately in each subgroup using the methods described above.

Analyses of post-randomization sub-groups are subject to many biases. Thus any analyses of post-randomization sub-groups would be considered on a case by case basis requiring tailored use of advanced statistical methods[36] and careful interpretation.

Missing Data
We expect no missing data for baseline measures. For 90-day assessments, extensive efforts will be made to ascertain the modified Rankin scores and mortality status, though we anticipate a 10% rate of lost to follow-up. We will perform several approaches for handling missing data. Characteristics of patients who are lost to follow-up will be compared to those that remain in the study to assess the degree of any selection bias, and sensitivity analyses will be performed to evaluate robustness of conclusions to the different missing data approaches. We will use multiple imputation for the final values assuming missing at random (MAR), depending on if any significant baseline differences exist between those observations that have a missing value or not. As sensitivity analyses we will report the data with and without imputation. Data will also be stratified according to their missing pattern (e.g., early termination, late termination, and follow-up completers) and variables representing these groups will be used as model covariates in adjusted analyses.

General trial logistical issues
We will descriptively (graphically) compare the hypothesized timeline for recruitment to the observed time line for recruitment and target range. We will also collect the following performance metrics of protocol compliance:

- Protocol deviations
- Missed/unable to screen subjects
- Volume of data queries
- Adverse events management

We will complete analyses of data quality including missing data, error patterns, protocol violations, etc. to determine if modifications in the protocol or data collection procedures or trial manual of operations are needed or to determine if the protocol itself can be followed. The SMC will review blinded data on recruitment, protocol deviations, data quality and adherence to study procedures, including a count of the number of instances when patients were not randomized.

Go/No go
The decision to complete the study will be based on the interim futility analysis. If we reject the null hypothesis (p-value<0.15), further study is not likely to be warranted.

12.b. Analysis Plan for Outcome S.A. 2: Determine the agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation.

We consider the on-site VN as the “gold standard”. Therefore, in determining if the remote VN can accurately replace the on-site VN, we will first test how often the on-site VN disagrees with the remote TM VN’s independent assessment of whether the patient should be treated with tPA. Second, if we eventually hope to have all physicians’ assessments on the MSU carried out solely by a remote VN using TM, we need to understand the variability inherent in assessing acute stroke patients for tPA on a MSU using this technology. An estimate of inter-remote VN agreement is challenging to ascertain due to ethical considerations of having another TM VN conduct an additional examination and thus possibly delay treatment. Therefore we will get an estimate of this variability by having a second TM VN review the video recording of the initial TM consultation, blinded to the final determination of the initial TM, to independently decide whether the patient should be eligible for tPA. The kappa between these two

observers and the agreement between the second TM VN and the on-site VN will be tested using the Kappa statistic.

Sample Size: The agreement between a VN remotely assessing a suspected stroke patient via TM in the MSU and in-person assessment by a VN in the MSU will be assessed by using the Kappa statistic. **We anticipate that an estimated sample size of 162 is needed to allow us 90 % power to detect 90% agreement between the in-person assessment and the TM.**

We will also identify and calculate the frequency of TM "failures" due to technical issues such as connectivity, CT scan access or image quality, ability to obtain sufficient history, adequate clinical exam, laboratory values, or other clinical information, and non-availability, etc. See TM CRF.

12.c. Analysis plan for SA 3: Cost Effectiveness Assessment.

Approach and Methods used in Cost Analysis

In order to establish an economic basis for a higher reimbursement from the healthcare payers for dispatching an MSU the following aspects have to be established:

1. Does the MSU improve the post-discharge stroke severity and consequently improve average patient QALYs? Higher cost for an intervention can be better justified if associated with improved patient outcomes.
2. Does the MSU reduce post-stroke healthcare utilization and consequently costs for the healthcare payers? Reduction of post-stroke healthcare utilization will subsequently save costs for the healthcare payers who pay for these utilizations. By identifying whether the healthcare payers save costs for stroke management due to the use of MSU (and determining the amount of post-stroke cost savings) the study can provide scientific evidence for supporting additional Medicare reimbursements for an MSU dispatch.
3. What is the magnitude of the incremental fixed costs associated with MSU and the per-patient incremental fixed cost due the ambulance outfitting, CT, other equipment, and telemedicine technology, staffing requirements and paramedic training? Establishing the magnitude of incremental fixed cost per patient will help determine the justifiable amount of increased reimbursements to agencies operating the MSU and providers supporting its telemedicine capabilities.

Sample used for Cost Analysis: The cost-effectiveness analysis (CEA) will include all enrolled patients on MSU and SM weeks who meet criteria for tPA treatment whether or not they are eventually treated with tPA. We estimate that approximately 50% of enrolled patients will receive tPA in the MSU and SM group. The non-tPA treated patients will probably not benefit much from MSU management and since the primary goal of the MSU is to ensure quicker administration of tPA, only those patients who meet criteria to receive tPA will be included in the cost analysis (for one year cost and QALY follow-up). The cost of operating the MSU for the remaining 50% of the patients who are not eligible for tPA administration will be included as fixed costs of operating the MSU, but these patients will not be followed-up once they are deemed ineligible to receive tPA inside the MSU or at the ED.

Perspective of the cost-effectiveness analysis (CEA): The CEA will be performed from the perspective of the healthcare payers. If dispatching an MSU improves patient outcomes it should theoretically reduce post-stroke healthcare utilization and hence the reimbursement costs for the healthcare payers under the current payment policies, which do not include additional reimbursement for an MSU dispatch. If the study demonstrates improved effectiveness along with cost-savings or demonstrates improved effectiveness with limited increase in costs for the healthcare payers it will help justify the additional reimbursements for dispatching an MSU. This justification is vital for the financial viability of this high cost intervention and hence critical for the study.

Measure of Effectiveness: Stroke results in severe morbidity, disability and mortality in the American population.[20] More than 70% of the stroke patients are unable to return to their pre-stroke life style, activities of daily living and employment. Thus, stroke has a permanent impact on the patient's QOL,

thereby necessitating the use of a **patient-centered effectiveness measure** that considers both the quality and quantity of a patient's life, and is not limited to physician reported clinical measures or survival. Hence, QALYs will be used as the effectiveness measure. QALYs will be obtained through utility-weight conversions using the EuroQol's EQ-5D measure. ED-5D is preferred due to its standardized ease of conversion to QALYs.[37,38] We considered the use of other QOL measures like Neuro-QoL. After communication with the Neuro-QoL research team it was established that Neuro-QoL has not been validated for conversion to QALYs. In addition, Neuro-QoL involves the reporting of 18 adult domains in the form of separate T-scores which should not be combined to form a single QOL measure further limiting the feasibility of QALY conversion. Since costs analysis requires QALYs and not QOL measures, Neuro-QoL and similar stroke-specific QOL measures, which cannot be converted to QALYs, are not used in this study.

Measure of Cost: The cost components include: 1) The incremental fixed costs associated with the MSU 2) The index hospitalization costs 3) The post-discharge cost during the first year after the stroke episode 4) Life-time costs after the first-year. The incremental fixed cost (component 1) for the MSU group will include cost of additional outfitting required to convert an ambulance into an MSU, cost of additional staffing changes for the agency operating the MSU, provider/hospital-level infrastructure changes to accommodate the MSU, clinical staff training, EMS and dispatch training, and all trips performed by the MSU (whether they involve tPA eligible patients or not). The variable cost (cost per patient) will include components 2 to 4, and will be measured for all patients in the MSU and SM group who meet criteria for tPA treatment whether or not they are eventually treated with tPA. Microcosting (resources * local market value) will be applied to the estimation of incremental fixed cost (component 1) whereas gross costing (utilization * Medicare payments) will be used for the variable costs of post-stroke healthcare utilization in the first year (components 2 and 3). Life-time costs after the first year (component 4) will be simulated using Markov modeling based on evidence from the literature.[25,26] The fixed cost of CT scanners and telemedicine equipment will be amortized over the 10 year expected life of the equipment. Medicare reimbursement amounts for patients from different geographic areas will be adjusted to make them nationally representative by using the CMS geographic adjustment factor (for part A claims) and CMS geographic practice cost index (for part B claims).

Outcomes for SA 3

Data Collection: Table 1 summarizes the data collection schedule. QOL information will be collected quarterly for 12 months after the stroke event in the form of EQ-5D. Cost/utilization data will be collected at baseline, discharge, and the end of 3, 6, 9 and 12 months. The UB 04 form from the hospital will be collected at discharge for estimating the utilization during hospitalization. The quarterly healthcare resource utilization information will involve face-to-face surveys before discharge and at the end of 3 months, and phone surveys at 6th, 9th, and 12th month. The surveys will be administered to both the patient and a proxy. Literature strongly supports the collection of utilization data every 3-4 months for complex chronic conditions in order to collect unbiased patient recall information,[39-41] hence this study collects patient-reported utilization information every 3 months.

Table 1: Details for cost and QALY information collection

DATA COLLECTION FOR COST			
Cost Components	**Source Used**	**Information included**	**Frequency**
Incremental Fixed Cost for the MSU arm	Cost and price quotes from the Frazer ambulance company and city of Houston (which procures and operates the	• Cost of additional outfitting required for the ambulance (including the cost of CT scanner and telemedicine equipment) • Cost of staffing changes for the agency operating the MSU • Provider level infrastructure changes to accommodate an MSU (including the	One time at the start of the study. Equipment costs will be amortized

	ambulance), and Cost information from the hospital administrators	telemedicine staffing requirements for the hospitals) and staff training • Trips performed by the MSU, whether or not the patient is eligible for inclusion in the cost analysis	over an expected life of 10 years.
Index hospitalization cost	UB 04 form	This form contains the ICD 9 diagnosis and procedure codes for services administered during the hospitalization and length of stay. This would include costs of IAT.	One time at the time of discharge
Post-discharge first year cost	Resource Utilization Form – Baseline (RUF-B)and Discharge (RUF-D)	The RUF-B and RUF-D will collect patient demographic, socio-economic and current healthcare utilization information at baseline and before discharge.	At or before discharge
Post-discharge first year cost	Resource Utilization Form – Follow-up (RUF-FU)	The RUF-FU will collect detailed information about health care resource utilization during the three months preceding the date when the form is filled. The RUF-FU will collect information on hospitalizations, skilled nursing facility stays, nursing home stays, rehabilitation center expenses, home health visits, therapy sessions, ER visits, ambulance services use, outpatient visits, primary care physician and specialist visits, drug use, laboratory tests, other diagnostic tests, durable medical equipment use, and home modifications, for up to one year after the index stroke episode, excluding the very first stroke hospitalization.	At 3, 6, 9 and 12 months after the index stroke episode
DATA COLLECTION FOR QALY			
Measure	**Instrument**	**Description**	Frequency
QALY	EQ 5D	Instrument measuring patient health state which will be used in conjunction with U.S. national utility weights for estimating QALYs gained.	At discharge, 3, 6, 9 and 12 months after the index stroke episode

Notes:

1. EQ5D should always be collected every time a RUF is collected (except at the baseline). So there will be 5 EQ5D forms.
2. In RUF 3rd 6th 9th and 12th months, question 1 and all its sub-parts (a to g) are associated with inpatient care, question 2 is associated with emergency care, question 3 is associated with outpatient care, question 4 is associated with ambulance service and question 5 with home health care.

The Specific Aims addressed to justify additional reimbursements for introducing and operating the MSU are as follows:

3.a Determine the cost-effectiveness of the MSU intervention from the perspective of healthcare payers under current reimbursement policies with no additional reimbursement for MSU dispatch.

To answer this question the CEA will be performed for the first year and life-time after stroke from the healthcare payer's perspective for the MSU and SM groups using the current reimbursement amounts. Healthcare payer costs will be computed based on the resource utilization of each patient multiplied by the corresponding Medicare reimbursement amount from the latest Medicare claims data. Stroke patients with similar average socio-demographic characteristics and baseline comorbidity scores as the study sample will be extracted from the Medicare claims and their average reimbursements for hospitalizations, skilled nursing facility stays, nursing home stays, rehabilitation center expenses, home health visits, therapy sessions, ER visits, ambulance services use, outpatient visits, primary care physician and specialist visits, drug use, laboratory tests, other diagnostic tests, durable medical equipment use, and home modifications will be used as cost amounts for each service utilization indicated in the resource utilization form.

Such an analysis which uses actual patient utilization multiplied by average national level Medicare costs for these utilizations has three significant strengths. The first is the external validity and generalizability of this measure. Since one of the limitations of this study is the geographic restriction to Houston area, examining cost savings in this area might not be applicable at the national level or to the CMS. By weighting the costs with national level reimbursement rates we can simulate the cost changes for Medicare due to the MSU management at the national level. The second strength is the ease with which this analysis can be adopted to examine cost changes from other perspectives. The utilization data obtained from our study can be multiplied by the corresponding costs of a particular provider or group of providers, health maintenance organizations, or private payers to perform a cost analysis from their respective perspectives. The third strength is the internal consistency of the measure. If a patient from the MSU group and one from the SM group with similar baseline demographic and clinical characteristics use the same level and types of services their post-stroke healthcare costs would be the same (and there would be no imprecision due to provider level variations in cost estimations). Hence, if the MSU leads to reduction in utilization the method will capture that accurately. In addition to all these strengths, our primary motivation to use this method is to understand if there are cost-savings from the healthcare payer perspective in order to build a case for additional reimbursements, thereby making this approach mandatory for the analysis.

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes used to extract patients with primary diagnosis of stroke from the Medicare claims data are provided below (events describing acute cerebrovascular disease which are unspecified have been excluded) in Table 2.

Table 2: ICD-9-CM codes for stroke patients

Clinical Diagnosis	International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes
ICD-9-CM codes for Ischemic stroke	
Occlusion and stenosis of precerebral arteries	433.0X (Basilar Artery), 433.1X (Carotid artery), 433.2X (Vertebral Artery), 433.3X (Multiple and Bilateral), 433.8X (Other specified precerebral artery), 433.9X (Unspecified precerebral artery)
Occlusion of cerebral arteries	434.XX
Other generalized ischemic cerebrovascular disease	437.1X (To answer a reviewer question – ICD-9-CM 436 cannot be included because it is "acute, but ill-defined, cerebrovascular disease, excluding both ischemic and hemorrhagic stroke". It includes events like seizures. 437.1X should be included as it is a type of ischemic cerebrovascular disease. For further validation please refer to reference 22 below for a detailed list of acceptable codes

	for ischemic and hemorraghic stroke.)
ICD-9-CM codes for Hemorrhagic stroke	
Subarachnoid hemorrhage	430.XX
Intracerebral hemorrhage	431.XX
Other intracranial hemorrhage	432.0X (nontraumatic extradural hemorrhage), 432.1X (Subdural hemorrhage), 432.9X (Unspecified intracranial hemorrhage)
ICD-9-CM codes for Transient cerebral ischemia	
Transient cerebral ischemia	435.XX

3.b Determine the cost-effectiveness of the MSU intervention from the perspective of healthcare payers if agencies and providers receive additional reimbursement for incremental MSU-related fixed costs per patient.

Incremental cost of introducing and operating an MSU as described in the table 1 above will be computed as an overall incremental fixed cost for the MSU arm. The CEA in specific aim 3.a will be re-performed from the healthcare payer's perspective assuming that the payer reimburses the incremental fixed costs associated with introducing and operating the MSU. This will help establish if the technology is still cost-saving or cost-effective for the CMS if the reimbursements are increased.

Analysis Plan

Although this study involves data collection for an exploratory CEA, a complete CEA analysis will be performed to get an estimate of the direction of the effect, and use the estimated parameters to accurately compute sample size estimates (if more data collection is required). The CEA will be performed as recommended by the task force of experts organized by the U.S. Public Health Service[37] and the International Society for Pharmacoeconomics and Outcomes Research.[42] We will perform both first year CEA and life-time CEA for MSU versus SM. To assess the cost effectiveness of our intervention, we will determine incremental cost-effectiveness ratio (ICER), which refers to the difference in the estimated mean cost between the MSU and the SM group divided by the difference in the estimated mean effectiveness (QALY) between the 2 groups. The base-case for the ICER will be the SM group. The 95% confidence interval for the ICER will be calculated to assess uncertainty through a nonparametric bootstrapping approach.[43] If the ICER replicates estimated during bootstrapping cover more than one quadrant of the cost-effectiveness plane, the cost-effectiveness acceptability curve approach will be used to capture the uncertainty.[44-46]

Apart from the ICER we will also perform the incremental net benefit (INB) analysis to assess the cost-effectiveness. The ICER ratio is negative if the cost associated with the intervention are lower and the QALY associated with the intervention are higher (a desirable outcome), or if the cost associated with the intervention are higher and the QALY associated with the intervention are lower (an undesirable outcome). Similarly, the ICER ratio is positive if the cost and QALY associated with the intervention are higher (a desirable outcome within bounds), or if the cost and QALY associated with the intervention are lower (an undesirable outcome). Hence the ratio's interpretation is counterintuitive if the outcome is undesirable. The INB addresses this problem by converting the QALY benefit into dollars.[47] The incremental QALY gained (or lost) due to the MSU is multiplied by the current valuation of 1 QALY (currently valued at $100,000 after inflation adjustment.[48-49] This dollar amount gained (or lost) due to the incremental QALY is considered a benefit and the increment cost due to MSU is subtracted from this amount to get the "net benefit" in dollar amounts. Thus when the INB is positive the outcome is desirable and when the INB is negative the outcome is undesirable. The INB estimate also lends itself to regression adjustments in case the MSU and SM group are not balanced in certain patient characteristics. The presence of right censoring and incomplete patient follow-up due to death or attrition will be tested and the inverse probability weighting will be applied to the INB estimation if required.[50-52]

We will also perform sensitivity analyses to determine the robustness of changes in values of the main parameters in the models on ICER and INB estimates. Deterministic one-way sensitivity analysis and multi-way sensitivity analysis will be performed by varying the parameters up to 20% in each direction. The main analysis includes the use of telemedicine to identify the stroke and initiate treatment in the MSU. An alternate analysis will be performed to examine the cost differences with no use of telemedicine but in-person assessment of the cases in the field by a neurologist who travels with the MSU.

The CEA estimates could lead to the following four scenarios and corresponding policy recommendations (note that with the increase in reimbursements for the CEA in column 3 there will be change in incremental cost but no change in incremental QALY) as described in Table 3.

Table 3: The four possible CEA scenarios

Scenario	Incremental Cost and Effectiveness in the CEA under the current reimbursement policies with no additional reimbursement for an MSU dispatch	Incremental Cost and Effectiveness in the CEA under the current reimbursement policies with additional reimbursement for an MSU dispatch	Conclusion and Recommendation
1	Intervention reduces cost and improves QALYs	Intervention reduces cost and improves QALYs	MSU dominates SM in all cases and should be additionally reimbursed
		Intervention increases cost and improves QALYs	The increase in cost is only due to the additional reimbursements. Implement and reimburse MSU if increase in cost is less than $100,000 per QALY.
2	Intervention increases cost and improves QALYs	Intervention increases cost and improves QALYs	The increase in cost is due to the additional reimbursement as well as higher utilization in the MSU arm. Implement and reimburse MSU if increase in cost is less than $100,000 per QALY.
3	Intervention reduces cost but does not lead to a statistically significant difference in the QALYs	Intervention reduces cost but does not lead to a statistically significant difference in the QALYs	The intervention is cost saving. MSU should be additionally reimbursed
		Intervention increases cost but does not lead to a statistically significant difference in the QALYs	The additional reimbursement does not result in cost saving. MSU is not cost saving or cost-effective.
4	Intervention reduces QALYs and the bootstrapping analysis establishes a statistically significant reduction in QALYS.	Intervention reduces QALYs and the bootstrapping analysis establishes a statistically significant reduction in QALYS.	Irrespective of cost changes the intervention is clinically undesirable.

Accounting for death rates in the MSU versus SM groups: In order to address some critical issues **on death rates raised by the reviewers we decided to add this additional paragraph to our cost-analysis.** Yes, it is true that patient death will imply that there are no subsequent first-year or life-time cost for the patient. However, patient death also implies that the subsequent QALY estimates are zero. If the MSU group has a lower death rate than the SM group, then the MSU group might have a higher

overall cost, however the MSU group will also have a higher overall QALY because of the higher number of life-years saved. The model implicitly accounts for cost and QALY changes due to differential death rates in both groups and will compute the incremental cost increase for every increase in QALY due to higher survival in either of the arms. It is important to remember that the intention of the cost analysis in this study is not just to compute cost-savings. The cost analysis also computes scenarios in which cost increases along with QALY and deems that outcome favorable depending on the extent of cost increase per additional QALY (Table 3). A second issue is the occurrence of random deaths in either arm which are unrelated to the disease under study. Since this is an exploratory cost analysis we will use non-stroke-related deaths to estimate possible loss in sample size, and compute the required sample size for the formal CEA in the phase III RCT using this exploratory data.

Sample Size Estimation for Cost Analysis: Since the current RCT is being designed as a futility study we'll perform an exploratory cost analysis using the cost data collected during this study. Based on the sample size estimation outlined in Willan et al[53], and cost and QALY estimations from past studies [54, 27, 25, 2], we estimated a range of sample sizes that will be required for a formal CEA. The lowest and highest observed change in QALY in the literature was 5-20%; similarly observed change in cost was 10-25%. Based on these the sample size requirement in the most optimistic case was 96 patients (48 in each group) and in the most conservative case was 740 pateints (370 in each group) for a power of 80% and p-value if 0.05. Approximately 50% of the patients for whom the MSU is dispatched, and who meet inclusion criteria for enrollment into the study, will receive tPA. Hence, the total number of patients used for the CEA will have to be between 192 and 1480 patients. Even though the current study probably will not meet the sample size requirement for the conservative case, the data from this exploratory study will be added to the future phase III RCT if the study is deemed "not futile". Since testing the cost-effectiveness hypothesis requires the maximum sample size among all the specific aims, due to high variance of the cost variable, collecting the cost data at this futily study stage will highly reduce the sample size demand on the future follow-up phase III RCT. Also, it will help establish the expected cost and QALY changes for the MSU intervention (which have never been estimated before) and hence improve the precision of the sample size estimation for the phase III RCT. We agree with the reviewers that "even though CEA is a secodary outcome it is a key outcome" and the phase III RCT will strive to meet the sample size requirements. To clarify a reviewer's question, the cost analysis cannot be one-sided because we are not just hypothesizing a reduction in cost and improvement in QALY. Cost could increase in association with an increase in QALY and this is also an acceptable outcome. We are testing outcome changes in both directions in the CEA.

13. Potential Biases

The ideal study design to test efficacy of MSU vs. SM stroke treatment would be a randomized clinical trial (RCT) in which the treatment assignment would happen in a randomized fashion either at the time of 911 call (MSU or SM pathway deployed) or after arrival on-scene when many stroke mimics or false-alarms can be ruled out. However in both of these scenarios, the MSU would need to be available or deployed on each and every possible stroke call. Unfortunately, this design is not feasible since we have only a single MSU and manning the unit 7 days a week every week would be cost-prohibitive. A valid criticism of cluster randomized trials is that bias can be introduced through the way patients are differentially recruited across treatment groups. Our pragmatic study will implement numerous design techniques to reduce this bias. First, eligibility for enrollment and tPA treatment will be determined in the pre-hospital setting on both SM and MSU weeks by the same investigators and using the same clinical criteria, **and both enrollment and tPA treatment will be adjudicated by an investigator blinded to MSU vs SM patient allocation**. Second, baseline comparability of clusters (patient co-morbidities, age, stroke severity) will be reported. Third, we plan an intention-to-treat analysis and will implement an aggressive protocol to reduce lost to follow-up and thus differential missing data. Finally, all outcomes will be measured by investigators blinded to treatment allocation.

Another bias might be introduced by the confounding effects of concommitant therapies such as heparin or endovascular treatment (IAT). Regarding concommitant therapy, we will discourage off-label use of drugs like heparin, but ultimately the day to day management of the patient once they reach the ED, Stroke Unit, ICU etc. will be in the hands of the Vascular Neurology team and outside the control of the MSU team. We will try to achieve standardized management by only admitting patients

to a VN service, by direct discussion of expected management between the VN team and the MSU team at the time of admission, by feedback from our study nurse who will be visiting the patients regularly during the first few days, and by asking these teams to adhere to published guidelines for stroke management[1]. One concern is excessive or imbalanced use of IAT. Recent clinical trials of IAT[14-17] have shown striking and consistent benefit in patients with severe strokes (median NIHSS 17, IQ 12-21), who have persisting large artery (ICA, M1, A1, proximal M2) occlusion in the anterior circulation after receiving IV tPA, have small core infarcts (median ASPECTS 9, IQ 7-10), were treated with the latest stentrievers, and had groin puncture at ~3.5-4 hours post onset. To date, 17% of our MSU tPA treated patients have received IAT, all of whom met criteria for IAT following our agreed upon protocol that closely approximated the criteria used in the recent positive clinical trials. We expect that this percent will increase somewhat as a result of additional data forthcoming this next year as they influence clinical practice. Once these data are available and digested by the stroke community, we will incorporate into the BEST-MSU trial the findings of a new standard of care for IAT as it emerges from these data. Until then, we will liberalize to 6 hours our previous protocol that had limited the time from symptom onset to groin puncture to 4 hours(see Appendix 3). Use of IAT in selected patients within this time frame is standard of care at each of our CSCs. Furthermore, shortening the time from symptom onset to start of IAT is one of the outcomes we will be measuring and may be an important advantage to the MSU. We will track the use of IAT, and expect that the two groups will be reasonably balanced in the proportion of patients receiving IAT (which we anticipate would be no more than 20% of each arm (MSU or SM)). However, we recognize that earlier treatment on the MSU might lead to more tPA success and therefore fewer IAT treatments in the MSU arm. Conversely, MSU management might increase the use of IAT by allowing more patients to be treated within the time window of possible IAT efficacy. Finally, SM patients may benefit from IAT obscuring some of the benefit of the MSU intervention. Since patients managed by either MSU or SM will have comparable access to IAT, any difference in the frequency of IAT between the arms would be a consequence of the effect of MSU vs SM management, and therefore will be important to measure and factor into our analysis. However, we will not be able to adjust for this post-intervention management, but rather need to consider it as part of „background therapy“ in this trial that compares MSU + background therapy to SM + background therapy. We will analyze our outcome and cost results exploring any confounding effect and then describe it, and we will also carry out a sensitivity analysis both including and excluding IAT patients.

Another concern is the choice of a dichotomous clinical outcome (mRS 0,1 vs 2-6). For reperfusion studies, this has been the outcome most commonly used and has been sensitive to the effect of tPA. Ordinal analyses are more complex and there remains some controversy how to analyze them. However, a substantial percent of our tPA treated patients have pre-existing disabilities, and it is impossible for these and more severely affected patients to ever achieve a mRS of 0 or 1. Recenlty, both utilitiy-adjusted and ordinal „shift“ analyses of the mRS have been used in clinical trials, and will also be employed in this study to enable assessment across the entire spectrum of outcomes seen in our patients.

14. Data Management

The subjects will be identified by a study number only. All hard copy source documentation will be kept in a secured, locked cabinet on site in the research coordinator‘s office. All study documents will be maintained in a secure location for two years following study completion unless superseded by participating site‘s requirement. The electronic data will be entered and maintained on a password protected web-based program designed for this trial.

The data entered for the trial will be maintained at the Data Coordinating Center (DCC) in a relational database cluster. The cluster is composed of multiple servers, which provide redundant access to the data in the event of a hardware failure to one of the servers. This cluster is maintained behind a firewall, which is not accessible from the internet without a secure network connection. The data will be backed up nightly and copies of the data will be routinely stored off site. In addition to the data servers, the production web server will also be backed up routinely. The separate development web server will serve as a backup to the production server.

Error Checking

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Checks will be developed by both clinical and DCC investigators. Depending on the question, any item found that does not meet the respective edit criteria will have an appropriate error message displayed when the user tries to save the data. Errors will be classified as either "hard" errors meaning that a valid response is required before the data can be saved or as "soft" errors in which the entry operator can either correct the errors or override them to indicate that the data are correct although it does not meet the edit criteria. Examples of hard errors would be items such as identifiers and event dates. An example of a soft error would be values that are outside a pre-defined range. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are currently four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors. For the first status, the entry user will have the option to save a record as "incomplete" for situations where they have partially entered a form and must stop because of an interruption. This will allow the user or the study coordinator to pull up the form at a later time and finish completing it. If the form was entered without any errors, then the record will be saved as complete. If the user overrides any soft errors found, the record will be saved as "saved with errors". Staff in the DCC will have web-access to listings of subject specific errors needing correction by site. These errors can be corrected at the site or in the offices of the DCC (given documentation of the change). All site investigators will be trained to follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once a follow-up about any errors has been done by the DCC and the error has been corrected or certified as accurate, the status will be change to "complete with errors." Once a record has been saved by the site or DCC as complete, they will no longer be allowed to make changes to the records. Any changes that result from obtaining new information would be made by the staff at the DCC. At the end of the trial after all possible corrections are made, the database will be locked and further changes will not be made.

Error Correction Follow-ups

Since there are times when data does not meet the required edit criteria such as out of range values, the site still needs to be able to save their data. However, such errors need to be followed up to ensure that the error was not by mistake. In this case, any soft error indicated will be logged to an error log data table through which the clinics can later generate a report of these errors that must be followed up on. This report will include the option for the clinic user to enter the correct value(s) if the record was saved by mistake or to indicate that the value saved was correct in which case they must provide an explanation as to why the error was overridden. These reports must be transmitted back to the DCC where staff will process the corrections through an error log management system. This process is particularly important for clarifying missing data. Once these reports are received back by the DCC staff and processed, the respective data record will be updated to the forth status of "complete with errors." Since clinical staff must verify these reports, these reports will serve as audit records should the funding agency need to investigate the process.

Data Sharing Plan

Once the database is locked for analyses and primary study publications are completed, the DCC will follow NINDS guidelines related to archiving de-identified data and making it publically available when requested by the NINDS. Furthermore, our protocol is designed is coordination with other centers in North American and Europe, with similar endpoints and study methodology to allow pooling of data.

Quality Assurance

Training of research staff and nurses who will be responsible for recruitment and randomization of subjects is planned for the BEST-MSU study and in line with standard procedures. A standard manual of operations (MOO) developed by the DCC's research team will provide standard definitions of all study variables (i.e., data elements) and describe all data collection and data entry procedures in detail. The manual will be used in training the site's research team and will be available on the study website. In addition to the planned training meetings, the site will be responsible for the complete education of their personnel in the conduct of the BEST-MSU study.

15. Adverse Events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject participating in a clinical trial. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not related to the trial intervention (in this case, use of the MSU).

An AE may be:

- New symptoms/medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/diseases existing before clinical trial start
- Recurrence of disease
- Increase of frequency or intensity of episodic diseases.

AEs fall into the categories "non-serious" and "serious".

Serious Adverse Event

A serious adverse event (SAE) is one that:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.

Adverse Event Observation and Documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject's medical records. In this trial, all AEs that occur after the subject has signed the informed consent document will be documented on the pages provided in the CRF. In addition, all AEs that occur pre-hospital either in the MSU or during EMS transport will also be recorded. All subjects who have AEs, whether considered associated with the use of the MSU or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up by the time of resolve or normalization of changed laboratory parameters or until it has changed to a stable condition.

The intensity of an AE should be assessed by the investigator as follows:

mild:	temporary event which is tolerated well by the subject.
moderate:	event which results in discomfort for the subject and impairs his/her normal activity.
severe:	event which results in substantial impairment of normal activities of subject.

The investigator will evaluate each AE regarding the coherency with the trial treatment possibly exist:

certain:	if there is a reasonable possibility that the event may have been caused by trial participation. A cartain event has a **strong temporal relationship** and an alternative cause is unlikely.
probable:	An AE that has a reasonable possibility that the event is likely to have been caused by trial participation. The AE has a **timely relationship** to the trial treatment(s) and **follows a known pattern of response**, but a potential alternative cause may be present.
possible:	An AE that has a reasonable possibility that the event may have been caused by trial participation. The AE has a **timely relationship** to the trial treatment(s); **however, follows no known pattern of response**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.

unlikely:	Only a remote connection exists between the trial treatment and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
unrelated:	An AE that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.
not assessed:	inadequate data for assessment, no other data may be expected

Reporting of Serious Adverse Events by Investigator

SAEs must be reported to the Data Coordinating Center, and the Principle Investigator within 24 hours after the SAE becomes known.

16. Ceretom CT Scanner

The operation and safety of the Ceretom CT scanner will comply with all state and institutional licensure and regulatory standards. The Ceretom machine will be operated by a certified radiology technician. All training and safety measures will comply with Texas Administrative Code 289.227, Use of Radiation Machines in the Healing Arts, Texas Regulations for Control of Radiation. The Safety, Inspection and Health regulations regarding the Ceretom machine will be managed by UT Health Radiation Safety Program.

Safety Manager, Radiation Safety Program
Environmental Health & Safety
The University of Texas Health Science Center at Houston (UTHSC-H)
6431 Fannin St CYF G102
Houston, TX 77030
713-500-5844

17. Liability

The legal and liability compliance of the operation and patient care on the Mobile Stroke Unit, delegated staff members and patient care and/or treatment will comply with all state and institutional licensure and regulatory standards. All legal and liability compliance regulations regarding the MSU will be managed by UT Office of Legal Affairs.

Office of Legal Affairs
7000 Fannin, STE 1460
Houston, TX 77030
(713) 500-3281

and

Memorial Hermann Lifeflight
Chief Operating Officer
6411 Fannin
Houston, Texas 77030
713-704-0006

18. Administrative Structure

Mobile Stroke Unit (MSU) Consortium. The MSU Consortium is responsible for the oversight of the Houston MSU. To enlist the cooperation of all parties including the hospitals, academic programs, and EMS, it is important that the MSU be a collaborative effort and not be "owned" by any one entity. Dr Grotta therefore formed the MSU Consortium which is comprised of all principle stake-holders in the Houston MSU program, and consists of UTHealth (the owner of the MSU), Memorial Hermann Hospital-TMC (the licensor of the MSU under its Life Flight program), other Comprehensive Stroke Centers in the TMC (that will receive patients and participate in the study), Houston Fire Department-Emergency Medical Services (who will collaborate with the MSU team in patient management), Dr. Grotta MD (who will oversee the operations of the MSU) and Frazer Limited (which has built and donated the MSU).

Mobile Stroke Unit Consortium Governance:

The MSU Consortium operates independently of any of its components. It has a **Steering Committee** comprised of representatives of its stakeholders. These include Elizabeth Noser MD (UTHealth), James H "Red" Duke MD (MHH-TMC, Life-Flight Medical Director), David Chiu MD (Stroke Program Director, The Methodist Hospital), Jose Suarez MD (Stroke Program Director, Baylor

Medical School/St Lukes Hospital), David Persse MD (Medical Director, HFD-EMS), James Grotta MD (Director, Mobile Stroke Unit Consortium), Laura Richardson (CEO, Frazer Ltd), and James McIngvale (Houston business community and principal donor). Dr Grotta is Chair of the MSU Consortium Steering Committee.

BEST-MSU Study Governance. The BEST-MSU study will be carried out under the umbrella of the MSU Consortium. The MSU Consortium Steering Committee with the addition of Jose-Miguel Yamal PhD and Suja Rajan PhD from the UT-SPH will comprise the **Steering Committee (SC**) for the BEST-MSU study. The SC will meet quarterly and will oversee the execution of the study and receive quarterly reports before each meeting from the Operations Committee and the Data Coordinating Center (see below).

The BEST-MSU Study day-to-day operations will be in the hands of an **Operations Committee (OC)** comprised of Drs Grotta and Noser, Tzu-Ching Wu MD (telemedicine), Stephanie Parker RN and Yvette Sanders (Administrator). The Operations Committee meets weekly and is in charge of MSU staffing, scheduling, maintenance, operations of the MSU and TM, and MSU team interaction with EMS and the Data Coordinating Center. The OC will provide quarterly reports on study conduct to the SC.

The BEST-MSU Study **Data Coordinating Center (DCC)** is comprised of Jose-Miguel Yamal PhD (Director), Suja Rajan PhD, Barbara Tilley PhD, Andrew Barreto MD, and J Grotta MD. The DCC will meet twice monthly and will be in charge of randomization, form development, database design and management, site training, monitoring and QA, and data analysis. The DCC will provide quarterly reports on data management and study conduct to the SC and Study Monitoring Committee. All communications from the DCC to the SC or OC will contain only masked data.

The BEST-MSU study will have a **Study Monitoring Committee (SMC)** comprised of David Lairson PhD Professor of Health Economics at the UTSPH (chair), Steven Levine MD, an international leader in Vascular Neurology and acute stroke treatment, telemedicine, and clinical trial conduct, and Robin Brey MD, Chair of Neurology at UT San Antonio and experienced clinical researcher and collaborator with Dr Grotta on telemedicine projects in Texas. The SMC will meet quarterly (by web) or more frequently if necessary, and receive the same quarterly reports from the DCC and OC that are sent to the SC, and will report to NINDS and to Dr Grotta any concerns or recommendations. The SMC will particularly focus on patient recruitment and retention, data integrity, protocol adherence, and safety issues, focusing on AEs and reasons for lost to follow up. In addition, the SMC will be available to the Steering Committee and Operations Committee for advice on any study related issues that arise.

19. Timeline

Year -1:	From 8/18/14-8/31/15. Enrollment of 70 tPA eligible pts.
Year 1:	(9/1/15-8/31/16): Enrollment of 70; 140 total
Year 2:	(9/1/16-8/31/17): Enrollment of 140 (70 Houston, 70 total from Denver and Memphis); 280 total
Year 3:	(9/1/17-8/31/18): Enrollment of 140 (70 Houston, 70 total from Denver and Memphis); 420 total
Year 4:	(9/1/18-8/31/19): Enrollment of 121(61 Houston, 60 total from Denver and Memphis); 541 total
Year 5:	(9/1/19-8/31/20): Follow up of Year 4 patients, data cleaning, lock and analysis; study publication and community dissemination

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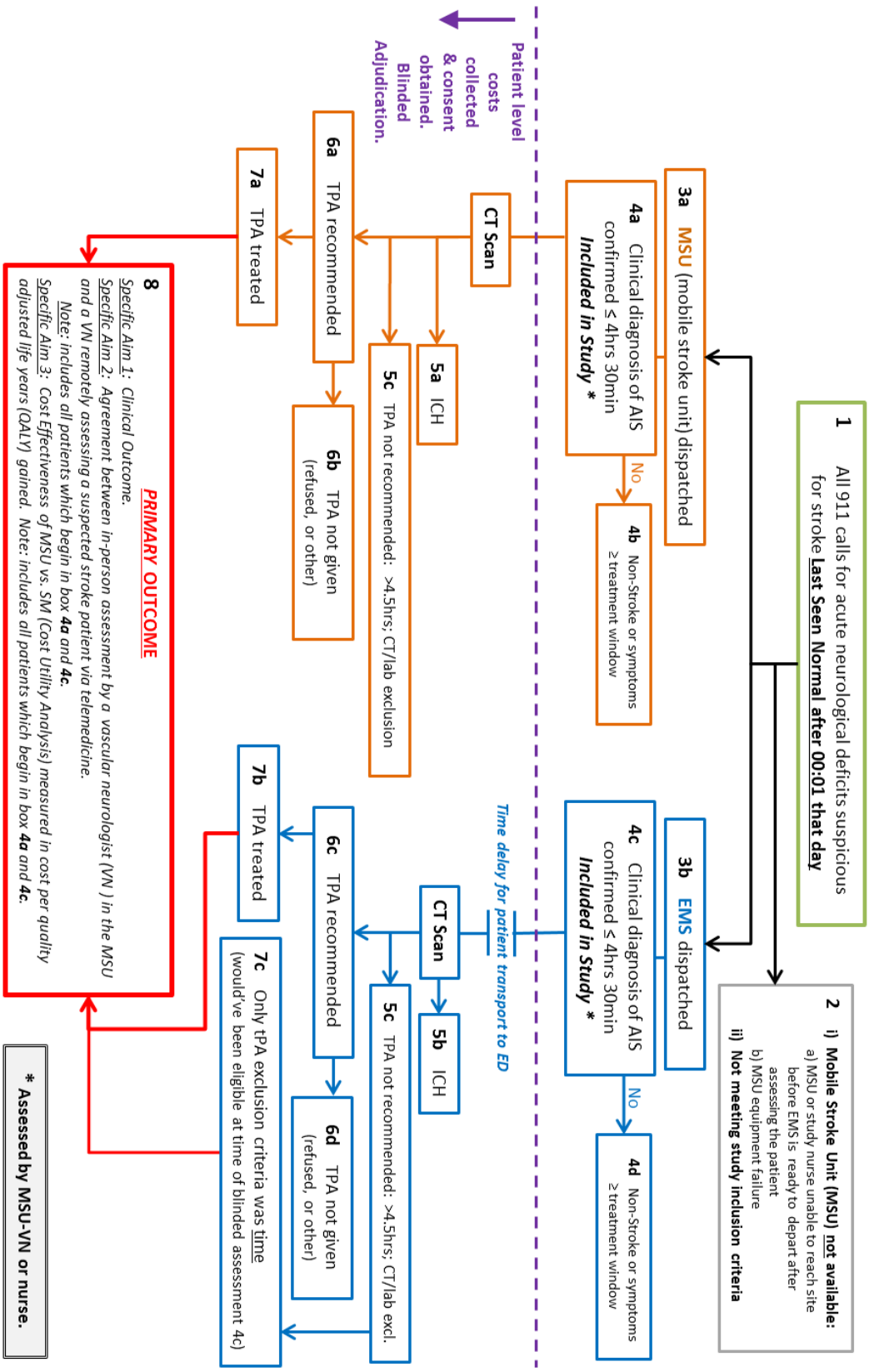
Appendix 1- Study Flow Chart



Appendix 2—Informed Consent

INFORMED CONSENT FORM TO TAKE PART IN RESEARCH

BEnefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study
(MOBILE STROKE UNIT)

HSC-MS-13-0322

INVITATION TO TAKE PART

You are invited to take part in a research project called, **BE**nefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study, conducted by James Grotta, MD, and collaborators at the University of Texas Health Science Center at Houston, Baylor College of Medicine, Memorial Hermann Hospital, St Lukes Hospital, The Methodist Hospital, Houston Fire Department Emergency Medical Services, West University Fire Department Emergency Medical Services and Bellaire Fire Department Emergency Medical Services. For this research project, he will be called the Principal Investigator or PI.

Your decision to take part, or continuing to taking part, in this study is voluntary. You may refuse to take part or choose to stop from taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from any hospital, physician or health care entity.

You may refuse to answer any questions asked or written on any forms. This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-13-0322.

PURPOSE

The purpose of this research study is to compare receiving standard emergency stroke treatment for ischemic or hemorrhagic stroke (a stroke caused by a blocked or bleeding artery in the brain) in a Mobile Stroke Unit (MSU), with standard emergency stroke treatment in a hospital, and to determine which has a better outcome and is more cost effective.

The standard, FDA approved emergency treatment for ischemic stroke is to give a drug called Activase®/Alteplase using an IV (in your vein). The standard in treating hemorrhagic stroke is to decrease systolic blood pressure to ≤ 150 with medications administered through the IV. With the help of a Mobile Stroke Unit, these treatments can be offered to patients having an ischemic or hemorrhagic stroke at the emergency site instead of at the hospital. This research study will try to determine if the mobile treatment option will save time and if it is safe. You are being invited to take part in the study because you may have experienced an ischemic or hemorrhagic stroke and a call was placed to 911 in order to provide assistance to you.

PROCEDURES

All treatment procedures completed during this study are standard of care. If you agree to take part in this study, or to continue to take part in this study, you will allow the research team to review some of your medical records from the treatment of your ischemic or hemorrhagic stroke, whether you were treated in the Mobile Service Unit (MSU) or at a stroke center hospital after being transported by the local Emergency Medical Service (EMS).

How the Mobile Stroke Unit Works
The MSU is dispatched along with EMS every other week in certain areas, during the hours of 8am to 11pm, Tuesday through Monday.

When the MSU is dispatched, standard treatment for ischemic or hemorrhagic stroke is given inside the mobile unit. This includes: a CT scan of the head, blood draws for lab tests, and treatment with, Activase®/Alteplase (depending on the type of stroke) and/or standard blood pressure medications. Afterwards, MSU ambulance will transport patients to the nearest stroke center hospital to continue care.

There are nine follow-up visits for this study. After 24 hours, a member of the study team will perform some cognitive tests, the National Institute of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (Rankin scale) to determine if you have had brain damage or have neurological deficits. The study team will also visit you on days 2 and 3, and the final day of your hospital stay to see if you have had or are still having complications. The study team will also call you by telephone to check on you at 30 days, ask that you come in to Dr. Grotta's clinic at 90 days after your stroke for a physical exam, and cognitive tests and call you by telephone at 6, 9 and 12 months after your stroke.

TIME COMMITMENT

The total amount of time you will take part in this research study is about 1 year after your stroke. Each study visit will last about 20 minutes.

BENEFITS

You may receive no direct benefit from taking part in this study. However, providing faster treatment within a Mobile Stroke Unit may reduce the negative outcomes associated with strokes.

RISKS AND/OR DISCOMFORTS

There are no additional risks to taking part in this research study other than those that are associated with the standard treatment for ischemic stroke. These risks will be explained to you by the physician that treats you or the PI. There is a possible risk of breach of confidentiality for taking part in this study.

ALTERNATIVES

The only alternative is to not take part in the study.

STUDY WITHDRAWAL

Your decision to take part is voluntary. You may decide to stop taking part in the study at any time. A decision not to take part or to stop being a part of the research study will not change the services available to you from Dr. James Grotta, emergency services, or area hospitals. The information obtained previous to withdrawal or study end will be used for data collection and analysis purposes; however the study team will not collect any more data after you withdraw from the study.

IN CASE OF INJURY

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Dr. James Grotta and to the Committee for the Protection of Human Subjects at (713) 500-7943. You will not give up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT AND COMPENSATION

You will not be paid for taking part in this study. All standard of care procedures will be billed to your insurance company. You will not incur any additional medical costs outside the standard of care treatment to participate in this study.

If you receive a bill that you believe is related to your taking part in this research study, please contact Stephanie Parker BSN, RN at 713-500-6116 with any questions.

CONFIDENTIALITY

You will not be personally identified in any reports or publications that may result from this study. Any personal information about you that is gathered during this study will remain confidential to every extent of the law. A special number (code) will be used to identify you in the study and only the investigator will know your name. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information.

You will not be personally identified in any reports or publications that may result from this study. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information.

NEW INFORMATION

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to stay in the study. This information will be provided to you during clinic visits or by phone.

Once the study is complete, the final results of the study will be sent to you via mail. A description of this clinical trial will be available on http://www.ClinicalTrials.gov NCT02190500, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at anytime.

QUESTIONS

If you have questions at any time about this research study, please feel free to contact Dr. James Grotta 832-325-7296 or Stephanie Parker, RN , BSN Project Manager at 713-500-6116, as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research.

AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH

PATIENT NAME:_____**DATE OF BIRTH:**_____

Protocol Number and Title: **BE**nefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study(HSC-MS-13-0322)

Principal Investigator: James Grotta, MD

If you sign this document, you give permission to The University of Texas Health Science Center at Houston, Memorial Hermann Healthcare System, Methodist Hospital, St. Lukes Hospital, Baylor College of Medicine, Houston Fire Department, West University Fire/EMS Department or Bellaire Fire/EMS Department to use or disclose (release) your health information that identifies you for the research study named above.

If you sign this document, you give permission to the researchers to obtain health information from the following health care providers:

Name of Provider	Address of Provider	Fax Number of Provider

The health information that we may use or disclose (release) for this research includes *all information in a medical record with the exception of personal identifiers (name, address or personal identification)*

The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston for the purposes of verifying research records. The researchers may also disclose information to the following entities:

- Food and Drug Administration (FDA)
- Data Coordinating Center –University of Texas School of Public Health

The University of Texas Health Science Center at Houston is required by law to protect your health information. By signing this document, you authorize The University of Texas Health Science Center at Houston to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. University of Texas Health Science Center, Memorial Hermann Healthcare System, St. Lukes Hospital System, Houston Fire/EMS, West University Fire/EMS or Bellaire Fire/EMS may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to:

Dr. James Grotta
Director, Mobile Stroke Unit Consortium
UT Professional Building
6410 Fannin St, Suite 1423
Houston, Texas 77030
Fax: 713 500 7014

This Authorization will expire 15 years after the end of the study.

SIGNATURES

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

_____
Printed Name of Subject or Legally Authorized Representative

_____ _____ _____
Signature of Subject or Legally Authorized Representative Date Time

_____
Printed Name of Person Obtaining Informed Consent

_____ _____ _____
Signature of Person Obtaining Informed Consent Date Time

CPHS STATEMENT: This study (HSC-MS-13-0322) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

Appendix 3- IAT Protocol

Original Approved Date: December 18th, 2012 Revised Date: March 20, 2013, February 15, 2015

Endovascular Protocol

1. Age ≥ 18
2. Baseline mRS ≤ 3
3. NIHSS ≥ 8 (done within 60 minutes of groin puncture)
4. CT--CT, CTA, ?CTP (done within 60 minutes of groin puncture)
   ASPECT Score ≥ 6
   Large artery occlusion (distal ICA, M1, A1, proximal M2)
5. Use of Stentrievers; avoid general anesthesia
6. Time
   < 1 hour qualifying CT and NIHSS to groin puncture
   < 6 hours symptom onset to presumed groin puncture in anterior circulation
   < 12 hours symptom onset to presumed groin puncture in posterior circulation

Appendix 4—ICH substudy

A Prospective study of early hemorrhage enlargement (EHE) and its treatment on the Mobile Stroke Unit (MSU) vs standard Emergency Department (ED) treatment (HEME-MSU Study).

Introduction and Background:

Active bleeding leading to hematoma enlargement (HE) occurs early after Intracerebral Hemorrhage.

Early studies conducted before the wide availability of CT scanning suggested that the period of active bleeding in ICH is rather brief (<1 hour),[1] and the observation of clinical deterioration after admission was frequently attributed to the effects of brain edema, although instances of continuous bleeding were occasionally reported.[2] A number of subsequent CT studies of the early phases of ICH have helped to clarify these concepts.

Broderick et al[3] evaluated eight patients with ICH by CT within 2.5 hours of onset and again several hours later (within 12 hours of onset in seven patients), documenting a substantial increase in hematoma size (mean percentage increase, 107%). This increase in the volume of the hemorrhage was accompanied by clinical deterioration in six of the eight patients, all of whom had a 40% increase in hematoma volume. In five patients, the clinical deterioration occurred with blood pressure measurements of 195 mm Hg or higher. These investigators suggested that a prolongation of active bleeding for several hours (up to 5 or 6 hours) after onset may not be uncommon as a mechanism of early clinical deterioration in ICH. Similarly, Fehr and Anderson[4] reviewed 56 cases of hypertensive ICH in the basal ganglia and thalamus and documented enlargement of the hematoma with CT in four (7%); in two of the four, the increase in hematoma size was documented within 24 hours from onset, and in the other two, it was documented on days 5 and 6. Three of the patients had neurologic deterioration. In two who experienced deterioration within 24 hours, it occurred in the setting of poorly controlled hypertension, whereas the others had adequate blood pressure control. One of two patients with adequate blood pressure control was a chronic alcoholic, leading the investigators to suggest that alcoholism may be a risk factor for delayed progression of ICH.

Three subsequent studies further clarified the patterns of early enlargement of ICH. Fujii et al[5] studied 419 patients with ICH, in whom they performed the first CT within 24 hours of onset and the follow-up CT within 24 hours of admission, which showed hematoma enlargement in 60 patients (14.3%). Kazui et al[6] conducted sequential CT evaluations in 204 patients with acute ICH, documenting enlargement of at least 12.5 cm^3, or by 40% of the original volume, in 20% of the cases. The highest frequency of detection of hematoma enlargement was seen in patients in whom the initial CT scan was performed within 3 hours of stroke onset (36%); the detection of enlargement declined progressively as the time from ICH onset to first CT increased, and there was no documentation of enlargement in those first scanned more than 24 hours after onset. These observations suggest that the period of hematoma enlargement can extend for a number of hours from onset as a result of active bleeding, which is a phenomenon that is frequently, but not always, associated with clinical deterioration. The study reported by Brott et al[7] involved 103 patients in whom first CT scans were obtained within 3 hours of ICH onset and follow-up CT scans were obtained 1 hour and 20 hours after the initial scans. ICH enlargement (>33% volume increase) was detected in 26% of patients at the 1-hour follow-up scan, and an additional 12% showed enlargement between the 1-hour and 20-hour CT scans. The change in hematoma volume was often associated with clinical deterioration, but there were exceptions. These researchers found no predictors of ICH enlargement, evaluating age, hemorrhage location, severity of initial clinical deficit, systolic and diastolic blood pressure at onset or history of hypertension, use of antiplatelet drugs, platelet counts, prothrombin time, and partial thromboplastin time. In addition to more frequent hematoma enlargement early after onset, a recent study showed that hematoma growth was also quicker (i.e. the bleeding was more rapid) the earlier after onset patients were imaged.[8] Finally, we have observed that HE is accompanied by a failure to mount the normal pro-coagulant response to bleeding as measured by thrombelastography (TEG).[9]

While these studies documented the importance of HE, and that it is more frequent and severe the earlier it is sought, no studies to date have evaluated HE in the first 1-2 hours after onset of ICH. Extrapolating from clinical data described above, it is very likely that HE will be even more frequent during the first hour after bleeding starts, and that interventions to limit bleeding might be most effective during this time interval. The advent of the Mobile Stroke Unit (MSU) where patients are evaluated and imaged within the first hour after onset of symptoms will make it possible for the first time to examine the natural history of this early hematoma enlargement (EHE), the use of TEG as a predictor of EHE, and the effect of interventions to limit it.

Aim 1: Use the MSU platform to evaluate the natural history of EHE

1a. We hypothesize that significantly more EHE will occur in the first two hours after symptom onset compared to later.

1a.i. The number of patients with EHE will be more.

1a.ii. The volume of EHE will be more.

All patients with ICH scanned on the MSU will have a repeat CT 1 hour after the initial CT. We will determine the number of patients with EHE, and the average volume of EHE, in patients scanned within the first 2 hours (and in the 0-1 hour and 1-2 hour groups separately), and compare results to those scanned 2-4 hours after onset.

1b. We hypothesize that there will be significantly smaller hematoma volume in patients having initial scan within 2 hours of symptom onset compared to those scanned 2-4 hours either on the MSU or in the ED.

Patients will be included if they have baseline CT carried out within 4 hours of symptom onset, whether initially scanned on the MSU or in the ED. The difference in average volume between those with baseline scan within 2 hours of symptom onset vs those scanned 2- 4 hours after onset will represent the average volume of EHE occurring during the time interval between the two populations (The 0-2 hour group will be analyzed as a whole, and also the 0-1 and 1-2 hour groups separately).

Rationale —HE is associated with worse outcome after either hypertensive or coagulopathic ICH. Most HE occurs within the first few hours after onset (see summary of literature above), but is probably grossly underestimated since patients are rarely seen and scanned within the first hour or so after onset when HE is most likely to occur. Early hematoma enlargement (EHE) occurring in the first 1-2 hours after bleeding onset may be much more frequent, proportionately larger in volume, and have a more important effect on outcome than HE during the ensuing hours. However, knowledge about EHE is limited as it is very rare to capture patients in this hyperacute period. MSU management will allow us for the first time to asses EHE.

Aim 2: Investigate the effect of early blood pressure (BP) control or coagulation reversal in ICH patients on EHE. Only patients with at least one SBP reading >150 or INR > 1.4 will be included in this Aim.

2a. We hypothesize that BP treatment (or coagulopathy reversal) within the first 2 hours after onset, as facilitated by the MSU, will reduce the number of patients having EHE.

2b. We hypothesize that BP treatment (or coagulopathy reversal) within the first 2 hours after onset, as facilitated by the MSU, will reduce the volume of EHE.

Patients will be included if they have baseline CT carried out within 4 hours of symptom onset, whether initially scanned on the MSU or in the ED. We will compare the number of patients who develop EHE and change in hematoma volume from baseline to 24 hours in patients having BP treatment (or coagulopathy reversal) begun within the first 2 hours after symptom onset (the 0-2

hour group will be analyzed as a whole, and also the 0-1 and 1-2 hour groups separately) to what is expected. Similarly, we will compare the same outcomes for those treated in the 2-4 hour group to the expected number of patients with EHE and expected change in hematoma volume. The expected incidence of EHE and amount of hematoma growth will be calculated based on what is observed from the untreated patients in SA1 and compared to their respective 0-2 hour or 2-4 hour group. The difference in number of patients with EHE, and in average volume, will represent the number of patients with EHE and the average volume of EHE prevented by earlier management. The proportion of patients in the 0-2 hour and 2-4 hour group treated in the MSU versus ED will be calculated.

Rationale --BP lowering is currently being tested to prevent HE after hypertensive ICH, and drugs are now available (4 Factor Prothrombin Complex Concentrate-4F-PCC) to rapidly reverse the coagulopathy caused by warfarin. Current standard management is to lower the SBP in our ED to 130-150 mm Hg or to give 4F-PCC for elevated INR once ICH is confirmed on CT scan. In both the aggressive and standard treatment arms of ATACH, patients will probably receive lowering of SBP to about 150 mm Hg (and lower in the aggressive treatment arm) after arrival to the ED. However, therapy begun in the ED will not result in BP lowering (or coagulopathy reversal) within the first hour of onset, and rarely within the first 2 hours. MSU management will permit such early BP lowering (or coagulopathy reversal) and allow us to assess its results on preventing EHE.

Aim 3: Determine if coagulation status, as measured by thromboelastography (TEG), is more altered very early after the onset of spontaneous (non-coagulopathic) ICH compared to later, and if TEG predicts EHE.

3a. We hypothesize that the pro-coagulation response to ICH will be greater soon after the onset of bleeding.

3b. We hypothesize that patients without early pro-coagulation changes on TEG will be more likely to develop EHE.

We will compare TEG values in MSU patients studied within the first 2 hours after symptom onset to those studied later, and in patients with EHE to those without. Patients with bleeding due to known coagulopathy or antithrombotic therapy will be excluded from this Aim.

Rationale -- We have shown that ICH is associated with faster and stronger clot formation as measured by TEG, but that patients with HE do not demonstrate this presumably adaptive response to bleeding. It is possible that failure to mount this hypercoaguable state after ICH may be important in leading to HE. This dynamic has never been studied in the first hours after ICH onset when EHE may be more frequent and dramatic than later HE. MSU management will allow us to obtain TEG measurements in the first hours after ICH onset and correlate them with EHE.

Inclusion Criteria:

1. Enrollment into MSU study (meeting all inclusion criteria)
2. Parenchymal ICH on first CT scan < 60cc
3. At least one SBP reading >150 or INR > 1.4 (only for SA 2)

Exclusion Criteria:

1. Primary or predominant IVH, SAH, or SDH
2. IVH with filling of >50% of the lateral ventricle

Interventions:

Group 1: Patients transported on the MSU found to have ICH on CT will receive protocolized BP treatment with Nicardipine or Labetalol to reduce SBP to 140-150 mm Hg in the MSU before arrival to ED (and treatment with 4F-PCC if INR > 1.4).

Group 2: Patients in the SM arm of the MSU study (no MSU deployment) later found to have ICH after CT in the ED will receive pre-hospital treatment as per EMS routine (control of SBP to no lower than 180 mm Hg using labetalol) followed by standard management of BP (or elevated INR) in ED

Primary Outcomes (All hematoma volumes measured by the AXBXC/2 method):

Aim 1:

1. Incidence of hematoma expansion(defined as increase in hematoma size by > 6cc or by 30%) and volume of EHE (ICH volume on 1 hour follow up scan – ICH volume on initial CT) in Group 1 patients who had initial CT scan within 4 hours of onset. 'EHE' will be used to indicate hematoma expansion occurring in patients captured within 2 hours from onset and 'HE' will be used to indicate hematoma expansion that is captured later. We will analyze the entire group of patients scanned within 2 hours as a whole, and also those scanned within 1 hour and between 1-2 hours separately, and compare with those scanned later. We will evaluate warfarin and non-coagulopathic related ICH patients separately.

2. Difference in average hematoma volume on baseline scans between 0-2 hour and 2-4 hour patients (Group 1 or 2). We will analyze the entire group of patients scanned within 2 hours as a whole, and also those scanned within 1 hour and between 1-2 hours separately, and compare with those scanned later. The difference in average volume will represent the average volume of EHE occurring during the time interval between the two populations. We will evaluate warfarin and non-coagulopathic related ICH patients separately.

Aim 2:

1. Incidence of EHE/HE and change in hematoma volume from baseline to 24 (+ 12 hr) hours in patients having BP treatment (or coagulopathy reversal) started within 2 hours and 2-4 hours of symptom onset (Group 1 or 2) compared to what is expected for each respective time group . We will analyze the entire group of patients treated within 2 hours as a whole, and also those treated within 1 hour and between 1-2 hours separately. We will also calculate the proportion of patients in each group with treatment begun on the MSU. The difference in number of patients with EHE, and in average volume, will represent the number of patients with EHE and the average volume of EHE prevented by earlier (mainly MSU) management.

Aim 3:

1. We will obtain TEG values (R, K, MA, Angle, Delta) in all Group 1 patients with spontaneous ICH (normal INR and no use of DTIs or Factor Xa inhibitors) comparing parameters in those with blood drawn within the first 2 hours versus 2-4 hours after symptom onset, and in patients with EHE to those without in the 0-2 hour group. We will analyze the entire group of patients analyzed within 2 hours of symptom onset as a whole, and also those analyzed within 1 hour and between 1-2 hours separately.

Other variables to be measured in both Group 1 and Group 2 patients:

1. Symptom onset time
2. Time of enrollment into either MSU or SM arm pre-hospital
3. Time of all CT scans
4. Hematoma volume, morphology and location on all scans
5. Etiology of ICH
6. Group 1: BP levels and treatment in MSU and ED for first 2 hours . Group 2: BP levels and treatment by EMS and ED up to the time of first CT scan
7. Time from symptom onset to first BP treatment and to first SBP < 150

8. Dose and time of any 4F-PCC
9. NIHSS at time of all CT scans (baseline in both groups, 1 hr CT in Group 1), and at 24 hrs in all pts.
10. Use of antiplatelet drugs
11. Significant comorbidities, chronic HTN, coagulopathy
12. TEG, other baseline coagulation measurements (platelets, INR, PTT)

Sample Size Estimation and Methods (All analyses adjusted for baseline NIHSS, use of antiplatelets, comorbidities; Use logarithmic transformation of hematoma volume to normalize the distribution):

Aim 1a. If we assume a 30% incidence of HE in the 2-4 hour group, and expect an increase to 60% in the 0-2 hour group, a total of 94 patients (47 per group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Aim 1b. Based on previous studies, the mean $\pm$ SD of the logarithmic hematoma volume in the 2-4 hour group should be 2.9 $\pm$ 1.2. If we expect 30% smaller baseline hematoma volumes in the 0-2 hour group log vol = 2.0), to achieve 80% power, a total of 64 patients (32 per group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Aim 2a. The expected incidence of EHE/HE and volume of hematoma growth will be derived from patients who present within 4 hours of onset (separated into 0-2 hour and 2-4 hour groups) who do not receive acute BP treatment or coagulopathy reversal. If we assume a 60% incidence of EHE in the 0-2 hour group and expect early BP treatment (or coagulopathy reversal) to reduce this to 30%, a total of 94 patients (47 per group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Aim 3. We have previously studied TEG values in ICH patients presenting within 6 hours of onset and compared TEG values for those who developed HE to those who did not. K, which represents speed of clot formation, was significantly slower in patients with HE, with a mean difference of 1.5 $\pm$ 3.1 min. Assuming mean K in the 2-4 hour group will be 1.5 min longer than the 0-2 group and that there will be a 1.5 min difference between HE and non -HE patients, then we would expect a 3 min difference between the 0-2 hour EHE patients and the 2-4 hour non-HE patients. A total of 40 patients (20 in each group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Procedures:

1. Get baseline MSU CT loaded onto PACS for measurement.
2. Obtain careful documentation of BP and BP treatment X first 2 hours Group 1 and up to time of first CT scan in Group 2.
3. Obtain accurate history of previous meds, comorbidities, coags, baseline NIHSS.
4. Obtain TEG in all Group 1 pts.
5. Obtain 1 hr f/u CT and NIHSS in all Group 1 patients.
6. Obtain 24hr CT and NIHSS in all pts.

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Appendix 5—Interosseous tPA administration substudy

Intraosseous administration of tPA for the BEST-MSU Study (IO-MSU Substudy)

I. Background and Rationale

The current protocol for HSC-MS-13-0322, the Be*nefits of Stroke Treatment Delivered Using a Mobile Stroke Unit Compared to Standard Management by Emergency Medical Services: The BEST-MSU Study,* requires intravenous (IV) administration of alteplase. In an urban prehospital setting, intravenous access by paramedics has an estimated initial attempt rate ranging from 77.4-89% success rate,[1,2] with an average time to insertion of 4.4 ± 2.8 minutes.[3] Intraosseous (IO) administration of medication offers an alternative to IV access in the prehosptial environment. Success rates for initial IO administration ranges from 84%-97% [4] [5] with the battery powered devices (EZ-IO) offering increased efficacy in speed of administration.[6]
Thrombolytics have been administered through the IO route safely for pulmonary embolism and myocardial infarction with no complications. [7] [8] The major concern for adverse effects relates to the potential for thrombolytic extravasation. Another case with both epinephrine and thrombolytic therapy through the IO resulted in significant soft tissue necrosis. [9] However the extravasation rates of drug administration from IO is a relatively rare occurrence if the needle is properly placed.[10] The goal of the emergency mobile stroke unit is efficacious and timely of administration of thrombolytic therapy.[11] This protocol addition to the current study will allow for IO placement and infusion of alteplase in patients who are unable to have an IV successfully placed after two attempts prehospitally.

Analysis

This protocol will utilize the patient level data collected from the BEST-MSU study. Only patients who had an IO placed with successful medication will be included. Analysis will include a report of the number of IV attempts made, the number of IO attempts made, and the record of success of infusion and in hospital complications related to the infusion.

II. Objectives

The primary objective of protocol is to provide IO as a route of alternative administration of alteplase in a patient without IV access.

Aims/Outcomes:

The investigators will assess the following outcomes from this protocol

- Number of IO lines place
- The number of successful infusions of alteplase via IO
- The number of complications related to IO infusion of alteplase.

In addition, this study will help to:

- Guide revisions or continued implementation of IO thrombolytic therapy both prehospital and in hospital.

III. Study Population

Inclusion criteria

All patients enrolled under the current HSC-MS-13-0322 trial who cannot have an IV placed successfully after two attempts.

Exclusion criteria:

- Infection of wound at site of IO placement
- Fracture or suspected fracture at IO site
- Previously attempted IO at site

IV. Protocol Design

All prior protocols from HSC-MS-13-0322 will remain unchanged. IV access will be attempted twice on a patient qualifying for alteplase administration based on the already established trial protocol. If

IV access is unsuccessful, IO access will be attempted using the EZ-IO device at the proximal tibia, just medial and inferior to the anterior tibial tuberosity. The treating physician or paramedic will be permitted a maximum of two attempts with IO. On second attempt the other tibial site must be used for placement. Prior to alteplase infusion, withdrawal and successful saline flush must be demonstrated to ensure proper IO placement. To reduce the pain that may be associated with initial infusion 10cc of 1% Lidocaine without epinephrine will be infused after verification of the IO line. The IO will be left in place until at least two hours after completion of the alteplase infusion. In the event of alteplase extravasation, the infusion will be stopped immediately, the IO will be left in place and saline will be infused through the IO.

V. Procedures

Data collection

The treating provider will report the number of IV and IO attempts if IV was failed to be placed

Data Analysis

Investigators will conduct data analysis to measure the outcomes and any adverse events associated with IO infusion

Reports and Publication

Investigators will participate in developing reports and research articles for academic and emergency medicine journals. Data will only be reported and/or published on an aggregated level.

VI. Benefits/Risks/Informed Consent

Benefits

Data generated from this outcomes research will potentially improve the care of stroke patients in the prehospital environment who require thrombolytic administration but are unable to have an IV established

Risks

The major risk is the potential for extravasation of alteplase through an incorrectly placed IO.

VII. References

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Appendix 6 – Genentech Safety Reporting

ASSESSMENT OF SAFETY

6.1 SPECIFICATION OF SAFETY VARIABLES

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to **Activase**, all events of death, and any study specific issue of concern.

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an medicinal product or other protocol-imposed intervention, regardless of attribution.
This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with treatment of acute ischemic stroke that were not present prior to the AE reporting period.

- If applicable, AEs that occur prior to assignment of study treatment associated with medication, no treatment run-in, or other ischemic stroke treatment.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

6.1.2 Serious Adverse Events

An AE should be classified as an SAE if:
It results in death (i.e., the AE actually causes or leads to death).
It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
It requires or prolongs inpatient hospitalization.
It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

6.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in Section 5.1.1, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

6.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 90 days following the administration of treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior treatment.

6.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately.

Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the **Activase** (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the **Activase**, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the **Activase**; and/or the AE abates or resolves upon discontinuation of the **Activase** or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the **Activase** (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to **Activase** administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

6.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

6.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinical visit?

"Have you had any new or changed health problems since you were last here?"

6.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). 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 ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. 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".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting 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 preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. 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 coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

- Hospitalizations for the following reasons do not require reporting:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
-

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior **Activase** exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

h. SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below.

The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682 or (650) 225-5288

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available. Serious AE reports that are related to the Activase will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date. Serious AE reports that are unrelated to the Activase will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date. Additional Reporting Requirements to Genentech include the following:

Any reports of pregnancy following the start of administration with the Activase will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date. All Non-serious Adverse Events originating from the Study will be forwarded on a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Appendix 6 – Genentech Safety Reporting (Cont'd)

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

BEnefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study

Trial Synopsis

Trial No.:	HSC – MS- 13- 0322
Title:	**BE**nefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study
Study Type:	Prospective multicenter cohort study with randomized deployment weeks and blinded assessment of both trial entry and clinical outcomes
Principal Investigator:	James Grotta, MD
Institute/ Department:	Memorial Hermann Hospital, Houston, Texas
Investigator:	James Grotta MD
Date of Protocol:	September 18, 2019 Version 9.0
Planned Dates of Trial	Start: August 18, 2014 End: June 30, 2021

Objectives: The primary goal of this project is to carry out a trial comparing pre-hospital diagnosis and treatment of patients with stroke symptoms using a Mobile Stroke Unit (MSU) with subsequent transfer to a Comprehensive Stroke Center (CSC) Emergency Department (ED) for further management, to standard pre-hospital triage and transport by Emergency Medical Services (EMS) to a CSC ED for evaluation and treatment (Standard Management-SM).

There are many ways that use of a MSU might prove valuable in stroke patients, but we will focus on acute ischemic stroke (AIS) and treatment with IV tissue plasminogen activator (tPA) within 4.5 hours of symptom onset since that is the most evidence based effective emergency treatment for the most prevalent stroke diagnosis. **We hypothesize that the MSU pathway will produce an overall shift towards earlier evaluation and treatment, particularly into the first hour after symptom onset, leading to substantially better outcome. We will also explore the hypothesis that as a result of improved clinical outcomes resulting from earlier treatment, the costs of a MSU program will be offset by a reduction in the costs of long term stroke care and increase in quality adjusted life years,** thereby supporting more widespread use of this technology. To make MSU deployment more practical, **we will confirm that a Vascular Neurologist (VN) on board the MSU can be replaced by a remote VN connected to the MSU by telemedicine (TM)** thereby reducing manpower requirements and costs.

The successful completion of this project will provide data on important outcomes and costs associated with the use of MSU vs SM in the United States (U.S.) that will determine the value of integrating MSUs into the pre-hospital environment that would be more generalizable throughout the country. Therefore, the proposed study is the necessary step in a process that may dramatically modify the way that acute stroke patients are managed.

No. of Clinical Sites: 7
No. of subjects:
To be assessed for eligibility (n = 10000)
To be enrolled (n = 2000)
To be analyzed ("tPA eligible") (n = 1038)

Main criteria for inclusion:

1. Criteria for MSU team to **enroll** a patient into the study (to be determined pre-hospital on both MSU and SM weeks)

    a. Last seen normal possibly within 4hr 30 min

    b. History and physical/neurological examination consistent with acute stroke

    c. No definite tPA exclusions per guidelines, prior to CT scan or baseline labs

    d. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment, including IV tPA, will not be delayed for consent; however, consent in both MSU and SM patients must eventually be obtained for data to be retained for analysis.

2. Criteria for **tPA-eligibililty** (to be determined pre-hospital on MSU weeks, and after ED assessment on SM weeks, and confirmed by blinded adjudication)

    a. Meeting tPA inclusion and exclusion criteria per guidelines after CT scan, baseline labs, and clinical re-evaluation

Test Procedure:	Pre-hospital diagnosis and treatment of patients with stroke symptoms using a MSU with subsequent transfer to a CSC ED for further management
Reference Procedure:	Pre-hospital triage and transport by EMS and treatment at a CSC ED

Primary endpoint:	1. Mean utility-weighted modified Rankin Scale (mRS) at 90 days, comparing patients found eligible for tPA (intention-to-treat based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU compared to SM weeks.
Secondary endpoints (in hierarchical sequence of importance):	2. The agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation. **N.B**. Patients will include all enrolled patients on MSU weeks considered for tPA treatment. 3. Determine health care utilization and QoL during the first year after the stroke on MSU vs SM weeks. 4. a. Mean utility-weighted mRS at 90 days,

	b. ordinal (shift) analysis of mRS at 90 days, and c. proportion of patients achieving 90 day mRS 0,1 vs 2-6 of enrolled patients treated with tPA within 60 minutes of LSN onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS) between the groups at the time of treatment. **N.B**. Patients will include only those patients actually treated with tPA based on the final determination of the time LSN, and will include only patients meeting all inclusion and exclusion criteria. 5. . a. ordinal (shift) analysis of mRS at 90 days, and b. proportion of patients achieving 90 day mRS 0,1 vs 2-6 6. comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU compared to SM weeks. The time from LSN to tPA treatment on all patients treated within 4.5 hours of LSN on MSU weeks compared to similarly eligible patients on SM weeks. **N.B**. Patients will include all enrolled patients actually treated with tPA (or on SM weeks eligible for tPA treatment) meeting all inclusion and exclusion criteria, and based on the final determination of time of LSN. One analysis will compare the median times. A second analysis will also capture the patients who were eligible but did not receive tPA because it was too late, categorizing time into the following groups (e.g., 0-60min, 61-90min, 91min-180min, 181-270min, eligible but no tmt because>270). 7. Of the enrolled patients that were eligible for treatment with tPA (according to published guidelines) on MSU weeks compared to SM weeks, the percent that were treated within 4.5 hours and within 60 minutes of LSN. 8. The time from LSN and from ED arrival to start of endovascular procedure (intra-arterial thrombectomy-IAT) in patients who meet pre-specified criteria for IAT onMSU weekscompared to SM weeks. **N.B.** All patients receiving IAT will be included in this outcome. 9. The median/mean time from LSN to tPA therapy decision on all patients considered for treatment within 4.5 hours of LSN on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patients meeting inclusion criteria whether or not treated with tPA. 10. Time between 911 call and onset of etiology-specific BP management on MSU weekscompared to SM weeks. **N.B.** Patients will include all enrolled patients.
Safety endpoints	**1.** The incidence of symptomatic intracranial hemorrhage (sICH) in enrolled tPA treated ptients on MSU weeks compared to SM weeks (Symptomatic intracranial hemorrhage defined as any intracranial blood accumulation associated with a clinical deterioration of ≥ 4 points of the N... which the hemorrhage

	has been identified as the dominating cause of the neurologic deterioration) **N.B.** Patients will include all patients treated with tPA, whether or not they meet all inclusion and exclusion criteria. **2.** Mortality. **N.B.** All enrolled patients signing informed consent will be included in this endpoint and followed until 1 year. **3.** The incidence of stroke mimics and transient ischemic attacks (TIAs) in tPA treated patients on MSU weeks compared to SM weeks. **N.B**. SM patients deemed eligible for tPA on their pre-hospital assessment who then completely recover by the time of arrival in the ED will equal the excess incidence of TIAs treated on the MSU pathway.

Pre-Hospital data to be collected:

1. Dispatch time
2. Arrival on scene time
3. Last seen normal time
4. Enrollment time
5. Baseline labs
6. CT time
7. tPA decision time
8. tPA bolus time
9. tPA infusion start time
10. First Blood Pressure treatment time and BP readings q5 min
11. Departure time from scene
12. On scene time—time from MSU arrival to time of departure to hospital
13. Time of hospital arrival
14. Distance from emergency site to point of MSU dispatch and to destination ED
15. NIHSS at time of tPA treatment and on ED arrival
16. CT scan result

Visit	1	2	3	4	5	6	7	8	9	10
Hour/Day Window	Baseline(= 1st physician/ neurologist contact)	24 Hrs. ± 2 Hrs.	48 Hrs. ±12 Hrs.	72 Hrs. ±12 Hrs.	Day 7 or Day of Discharge	30 Days ± 7 days	90 Days -7/+30 Days	6 month -7/+30 Days	9 Month -7/+30 Days	12 Month -7/+30 Days
Demographics	X									
Medical History	X						X			
In-/Exclusion Criteria	X									
Informed Consent and subject Information	X									
Vital Signs	X									
Thrombolysis as indicated	X									
Adverse Events	X	X	X	X			X			
CT Scan#	X##									
NIHSS	X	X					X			
Modified Rankin** Scale	X				X	X	X			
Study Completion Record							X			X
Resource utilization information	X				X		X	X	X	X
EQ-5D - QALY					X		X	X	X	X

Fig.1 Flow Chart

Follow up CT or MRI imaging is optional as is the timing (except in ICH patients—see below). It will be carried out as per routine care and results will be recorded if done. CT or MRI will be immediately performed in the case of neurological deterioration.

In patients who may be endovascular candidates, CT angiography (CTA) may be done as well. In ICH patients, CT scan to be repeated after 1 hour in all MSU patients, and after 24 hrs in all MSU and SM patients.

** Pre-stroke mRS will be determined; Telephone mRS ok at 30 days

† Details about all the resource utilization forms and quality of life measurement forms, and their timeline are provided in Table 1

Table of Contents

1. Background.

We propose a randomized comparative effectiveness study of two pre-hospital strategies for managing stroke patients: earlier diagnosis and treatment using a Mobile Stroke Unit (MSU) vs. standard triage and transport by Emergency Medical Services (Standard Management-SM). We will focus on treatment of patients with acute ischemic stroke (AIS), the most prevalent stroke diagnosis, with intravenously administered tissue plasminogen activator (tPA), the only effective pre-hospital/emergency treatment.

1.A. Impact of stroke on individuals and populations. Stroke is the 4th leading cause of death and leading cause of serious long-term disability in the U.S. Every year, more than 795,000 people in the U.S. have a stroke with one new stroke occurring every 40 seconds[1]. It is projected that by 2030 4% of the American population would have had a stroke. Stroke incidence is particularly high among younger African-Americans, lower socioeconomic groups, and in the Southeast U.S. including east Texas and Tennessee, two of the seven centers in this proposal[2]. More than 70% of stroke patients are unable to return to their pre-stroke life style, activities of daily living and employment. AIS results from a blood clot blocking an artery to the brain and accounts for 87% of all strokes. Intravenously administered tPA is a highly effective treatment for AIS that can be carried out in the pre-hospital or Emergency Department (ED) setting[3]. Clinical trials consistently confirm the relationship of treatment success with decreased time from last-seen-normal (LSN) to initiation of treatment[4-8]. However, despite two decades of efforts to streamline Healthcare systems, most patients are treated beyond 2 hours, since treatment has been ED-based and the median door to needle times in stroke center EDs in the U.S. approximates 60 minutes[9,10]. Such delay contributes to the overall low national tPA treatment rate--about 5% of all AIS, with only 0.0005% or 1 out of 2,000 stroke patients treated within the first hour after onset. Recently, substantially faster treatment with tPA became a reality after German researchers placed a Computed Tomography (CT) scan and physician on an ambulance with treatment safely "taken to the patient"[11]. This MSU increased treatment rates from 21% to 33% with 25 min shorter time to treatment[12]. Thirty-one percent of MSU tPA patients were treated within 60 minutes of onset compared to 4.9% with Standard Management (SM), and these patients had an OR of 1.93 (95% CI 1.09-3.41) of discharge to home compared to later treatment[13]. In addition, recent transformative trials[14-17] have shown substantial benefit from intra-arterial mechanical thrombectomy (IAT) for patients with the most severe strokes, and also demonstrate that patients who achieve recanalization quickly benefit most. MSUs might speed IAT by allowing prehospital identification of appropriate patients and shortening in-house delays incurred by acquiring imaging/labs, treating with tPA, and assembly of the IAT team, perhaps allowing bypass of ED evaluation altogether. Therefore, the MSU strategy may substantially improve outcomes for patients with AIS, and dramatically alter the Healthcare system for all acute stroke patients.

1.B. Gaps in evidence. Speeding acute stroke treatment, and in particular tPA administration is among the highest stroke research priorities. The top priority recommendation for acute stroke of the 2013 NINDS Stroke Progress Review Group (which included consumer advocates) was "Making reperfusion therapy swifter, safer, and surer"[18]. The 2013 and 2015 guidelines on acute stroke management[1,19] state: "Patients should be transported rapidly to the closest available certified primary stroke center or comprehensive stroke center… *(Class I; Level of Evidence A)*", and "Systems should be designed, executed and monitored to emphasize expeditious assessment and treatment." Gaps our study will address include: 1) There has been no comparison of longer-term patient-centered outcome between MSU and SM. 2) There is no experience using the MSU in the U.S., where traffic patterns, distances, market forces, and local Emergency Medical Services (EMS) and ED regulations may affect the Healthcare system implementation of MSUs. 3) There are no data on how much added benefit derives from tPA treatment within the first hour after LSN. This information can only be obtained by pre-hospital treatment using an MSU. 4) There are no data on the impact of MSU management on IAT, specifically how many more patients can access IAT within the timeframe of evidence-based benefit. 5). Although a comparative effectiveness trial has not been completed yet and therefore there is a lack of the necessary rigorous evidence to support implementation of MSUs, several U.S. cities have already purchased MSUs.

2. Significance

2.A. Potential for improving health care and outcomes. If our study shows the hypothesized benefits of the MSU strategy, we foresee MSUs embedded in EMS ambulance fleets throughout the U.S. In urban areas, we foresee 1 MSU strategically located approximately every 500,000

population, dispatched to stroke calls after a 911 call or when a stroke is identified by a first responder, staffed by three paramedics or two paramedics and a nurse, crossed trained in performing CT scanning, and in communication with a remote Vascular Neurologist (VN) via Telemedicine (TM). MSUs would leverage centralized TM support, and their deployment would be tailored to the specific environment. In a more rural setting, a larger percent of calls would involve "rendezvous" of the MSU with an ambulance delivering the patient from a distance. Our study will provide solid outcome data resulting from MSU utilization, reflecting the value that stroke patients and their caregivers place on quality of life as well as "hard" measures of healthcare utilization. Such data will be important to patients and caregivers by reinforcing the need to be alert to stroke symptoms and signs and to call 911 should they occur. This message is easier to deliver and more likely to change behavior the more evidence we have that it makes a difference in patient-centered outcomes. The data will also be valuable to payers, legislators, regulators, hospital and EMS administrators, MSU manufacturers, other providers of pre-hospital care and equipment, endovascular providers, patient support groups, and other stakeholders that re-orientation of our Healthcare Systems to accommodate MSUs is worthwhile.

2.B. Focus on outcomes of interest to patients and caregivers. The primary outcome is the change in utility-weighted modified Rankin Scale (Δ uw-mRS)[20] from baseline to 90 days in patients found eligible for tPA on MSU weeks compared to SM weeks. The uw-mRS assigns values to each mRS grade depending on patients' value of that level of function, with lower mRS scores (reflecting less disability) given proportionately higher weight than higher mRS scores (reflecting more disability). This patient centered endpoint is being utilized in the DAWN stroke trial[21]. By calculating the change in uw-mRS from baseline to 90 days, we can include, and calculate the effect of treatment, in patients with pre-existing disability who were excluded from all previous stroke treatment trials which focused on achievement of non-disabled outcome. Quality Adjusted life Years (QALYs obtained through utility-weight conversions using the EuroQol's EQ-5D measure) is a patient-centered effectiveness measure that considers both the quality and quantity of a patient's life. EQ-5D and healthcare utilization data will be collected quarterly for 1 year post stroke from patients and caregivers.

2.C. Overview of Research Strategy. This study is a comparative effectiveness trial of outcomes in patients having pre-hospital management employing a MSU vs comparable patients having "standard" pre-hospital management. Weeks when the mobile stroke unit is available (MSU weeks) or not (SM weeks) are randomized. Faster treatment of AIS patients with tPA and subsequent triage of selected tPA-treated patients for IAT are the only evidence-based effective interventions that may differ between MSU and SM management. Therefore, tPA eligible AIS patients will be the subjects compared. We hypothesize that in tPA eligible patients, MSU management will result in improved patient-centered outcome of the uw-mRS assessed at 90 days after enrollment, and QALYs and healthcare utilization assessed for the first year after the primary stroke hospitalization. Research associates gathering outcome data will be blinded to group assignment. The study includes a Clinical Coordinating Center for coordinating patient enrollment and study operations, a Data Coordinating Center that independently manages the database, assures data quality and performs all analyses, a Steering Committee, and a Study Monitoring Committee/DSMB.

3. Specific Aims

3.A. Specific Aim 1: Compare the clinical outcome of patients meeting criteria for tPA treatment on the MSU vs SM**.**

Outcome (Mean uw-mRS at 90 days) of patients meeting guideline criteria for tPA treatment managed on MSU weeks compared to similar patients on SM weeks.

Context: already described above

3.B. Specific Aim 2: Determine the agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation**.**

Outcome: Agreement between on-site and remote tPA decision-making, and percent of consults completed without technical failures.

Context: Eventually, the widespread use of MSUs will depend on adequate manpower to guide treatment. Our preliminary experience, and data from Germany, suggest that the ratio of MSU "alerts" from EMS dispatch to tPA treatments is at least 10:1 making it impractical to have a VN on board the MSU for all calls. However, the decision whether to give tPA based on clinical criteria requires training, experience, and careful judgment. Recently, we have demonstrated the feasibility and accuracy of TM assessment of actors simulating stroke patients in ambulances usi technology[22]. However,

TM has not been tested for treating actual stroke patients with tPA in the pre-hospital environment. By simultaneous TM evaluation of the stroke patient on-scene using a monitor mounted on the MSU gurney and facilitated by the MSU paramedic, we will compare the diagnostic and tPA-related treatment decisions made by the on-scene VN to those made by a VN at the hub assessing the patient via TM. We will also measure the rate of technical failures in conducting the TM consultation.

3.C. Specific Aim 3: Determine health care utilization during the first year after the stroke on MSU vs SM weeks. .

Context:

3.C.1. Economic Impact of Stroke: Stroke is among the top 15 most expensive conditions treated in the US hospitals, and among the top 10 most expensive conditions billed to Medicare.[23,24] Medicare bears the highest cost burden of the disease; almost 60% of stroke-related hospital costs and more than 60% of overall stroke-related costs are borne by Medicare. [24,25] Non-nursing home stroke care constitutes more than 10% of Medicare's budget [26]. As the US population ages, the incidence and prevalence of this disease will increase, and hence costs associated with stroke and the cost burden of Medicare will substantially increase. It is projected that by 2030 4% of the American population would have had a stroke and the total medical cost of stroke will be nearly $200 billion (2010$), which is a 250% increase as compared to the medical costs as of 2012. [27]

3.C.2. Economic evaluation of tPA: Ischemic stroke accounts for 87% of all stroke events. The early use of tPA has been shown to be both clinically efficacious and cost-effective. Fagan et al [28] demonstrated that the use of tPA (as compared to placebo) reduced hospital length of stay, with higher discharge to homes instead of inpatient rehabilitation or nursing homes. Their Markov analysis predicted an increase in quality adjusted life years (QALYs) with 94% probability and a decrease in post-stroke first year costs with 93% probability among patients receiving tPA. In another study, tPA use within 4.5 hours of stroke occurrence had an ICER of $1478/QALY (in Australian currency) during the first year but also marginally increased costs[29]. Tung et al [30] performed a life-time cost effectiveness analysis for the use of tPA and found an increase in both life-time costs and QALYs with tPA administered within 4.5 hours of ischemic stroke, with an ICER of $21,978/QALY.

In spite of the benefits associated with tPA, the drug is used in a very small proportion of stroke patients [31,8,9] because of the small window of opportunity for its administration. Demaerschalk et al [31] showed that if tPA was used in 20% of stroke patients it would save $74 million in medical costs during the first year after the stroke event. This amount is 10 times more than the amount saved with the current tPA use of 2-4%. The technology proposed in our study strives to reduce the time from stroke onset to treatment initiation thereby increasing the probability of tPA administration among ischemic stroke patients.

4. Preliminary Data

4.A. Steps in establishing the MSU

We introduced at the Texas Medical Center in Houston the nation's first MSU funded by donations from Dr Grotta's grateful patients, local philanthropists and the Frazer ambulance company. Not only are we the first center in the U.S. to put into operation an MSU, but we are the first (and only) group to employ it for clinical research purposes.

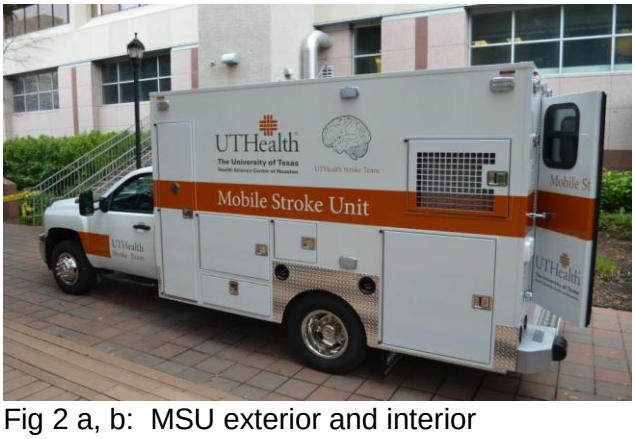


Fig 2 a, b: MSU exterior and interior

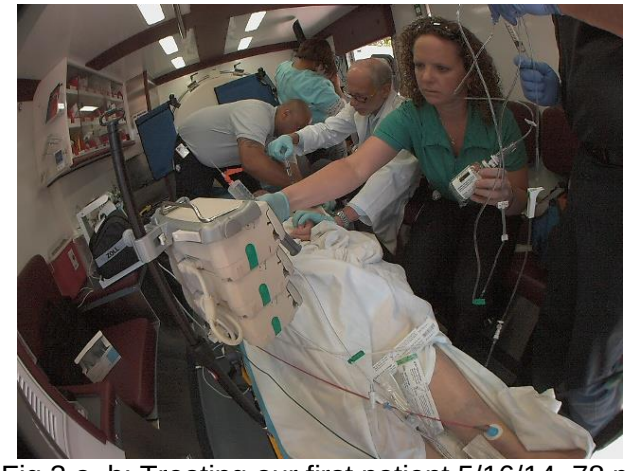
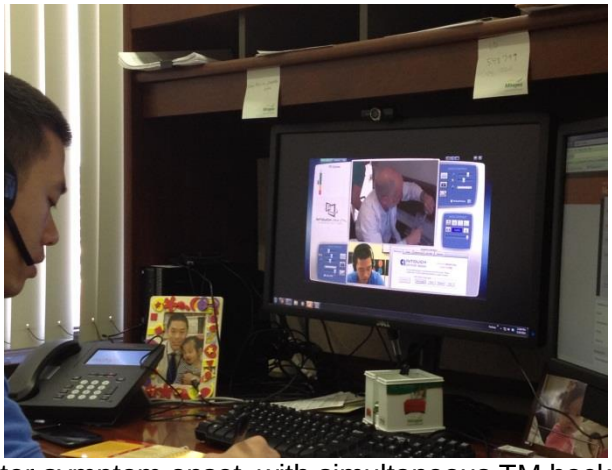



Fig 3 a, b: Treating our first patient 5/16/14, 78 min after symptom onset, with simultaneous TM backup

4.A.1. Conceptualization, Funding, and Build-out of the Houston MSU. The Houston MSU project was initially formulated after Dr. Grotta visited Drs Fassbender and Walter and then subsequently Dr Audebert in Berlin in 2012. Since there was no established pathway to implement a MS in the U.S., the following steps were begun more or less chronologically in March 2013.

- $1.8M was raised mainly from grateful patients, community philanthropists, and industry partners.
- Frazer Limited donated the ambulance "box" to UTHealth. Frazer Limited is located in Bellaire Texas, about 5 miles from the TMC.
- The CT scanner was purchased from Neurologica. Some equipment (cardiac monitor) and supplies were donated by Memorial Hermann Hospital (MHH), but most (ambulance chassis, stretcher, pumps, drugs, remaining supplies) were purchased from funds raised.
- The MSU was constructed at the Frazer factory—see links: http://www.frazerbilt.com/Videos/watch.php?id=784 https://www.youtube.com/watch?v=y1m64EL-k5I&index=6&list=UU7MwkvzzoUJ1SOHHl-PvLBQ
- Dr Grotta resigned his position as Chairman of the Department of Neurology to direct this project, form a consortium of local stakeholders, and apply for funding to enable completion of the study. Dr Grotta became employed by MHH and was provided 80% time to oversee operation of the MSU and the coordination of this clinical trial, as well as liability insurance covering his activity on the MSU.
- David Persse MD, medical director of the Houston Fire Department Emergency Medical Services (HFD EMS) was enlisted as a collaborator.
- The MSU staff-Project Manager (Stephanie Parker RN), CT technician, and 5 licensed Paramedics, along with part time VNs and RNs, was hired and on-call schedule developed.
- The MSU team became housed on the 14th floor of the UTHealth Professional Building (UTPB) located within 1 city block of all 3 CSCs, and the MSU parked in a dedicated spot in the driveway of this building with routing of appropriate power supply.

4.A.2. Licensing, Insurance, Contractual arrangements, and Institutional review

- The MSU was leased from UTHealth by MHH and licensed under a Texas state private ambulance provider's license held by MHH and its Life Flight helicopter ambulance service. MHH covers the insurance for MSU operations in case of accidental injury to patients or personnel. Patients carried by MSU are registered within the MHH system.
- The MSU passed both state and city ambulance inspection.
- A Clinical Trial agreement between UTHealth, MHH and the City of Houston and an exception to a city ordinance was signed by the mayor allowing transfer of patients from the city's EMS to the MSU.
- All physicians, nurses, paramedics and radiology technicians staffing the MSU hold appropriate Texas state practitioners licenses, passed Advanced Cardiac Life Support training, and have liability insurance.
- The MSU study protocol was approved by the Committee for the Protection of Human Subjects (CPHS) at UTHealth (HSC – MS- 13- 0322).
- We were informed by the FDA that an IND is not required for th dy.

4.A.3. Collaborations with regional stroke centers.

- The directors of the CSC Stroke Programs at St Lukes and Methodist Hospitals, and at the VA Hospital (Drs Suarez, Chiu, and Kent) agreed to collaborate and actively participate in the MSU study.
- The stroke teams and EDs at the destination CSCs agreed to adhere to the protocols to select patients for tPA and IAT treatment.

4.A.4. Collaboration and training of EMS

- The MSU is operated in collaboration with 3 EMS organizations; HFD EMS as well as EMS from West University Place and Bellaire, two subdivisions within Houston that are adjacent to the TMC.
- The MSU team met with and in-serviced the dispatch centers and paramedics from these EMS organizations, and a communication system was established.

4.B. PURSUIT Study (T.Wu P.I.)**.**

In the PURSUIT (Pre-hospital Utility of Rapid Stroke evaluation Using In-ambulance Telemedicine) study, we explored the feasibility and reliability of using TM in the ambulance to help evaluate acute stroke patients. Trained actors portrayed ten unique stroke scenarios, each conducted four times, and were retrieved and transported by HFD-EMS to our stroke center. A remote VN, based at UTHealth performed remote assessments in real-time and obtained clinical data points and NIHSS using the In-Touch RP-Xpress device. In 34/40 (85%) scenarios, the teleconsultation was conducted without major technical complication. The absolute agreement for intra-class-correlation (ICC) was 0.997 (95% CI: 0.992-0.999) for the NIHSS obtained during the real-time sessions. Matching of real-time assessments occurred for 88% (30/34) of NIHSS scores by ±2 points, and 96% of the clinical information[22].

4.C. Run-in phase. The Houston MSU went into service in May 2014. We planned a "run-in" phase to perfect our various alert mechanisms from EMS dispatch and on-scene EMTs, practice our on-scene interaction between the MSU team and the EMS squad including rendezvous, practice tPA administration and other patient management issues on board the MSU, get a preliminary evaluation of TM reliability, and rehearse our SM week interaction with EMS. The run-in phase included 9 MSU weeks and 2 SM weeks. During the MSU weeks, we were alerted 90 times, and enrolled and transported 25 patients. Reasons for non-enrollment mainly included time/wake up, hypoglycemia, syncope, TIA, seizure, migraine, and "other". During the run-in phase, we treated 13 patients with tPA on the MSU, and another patient met criteria for tPA treatment during the two SM weeks. Of the 13 tPA treated MSU patients, 31% were treated between 0-60 minutes from LSN, 38% between 61-90 minutes, 15% between 91-180 min, and 15% between 181-270 min. Of the 12 patients who were transported but not treated, the reasons for non-treatment were: 4 ICH, 3 seizures, 1 LSN >4.5 hrs, 1 SDH, 1 mimic, 2 TIA. Our average "on-scene" time for MSU transports was 28 min (range 12-53 min), with average alarm to treatment interval of 52 min (range 37-156 min). The one SM tPA eligible patient was treated in the ED during the 61-90 min interval from LSN. Of note, 4 of the 13 tPA treated patients on the MSU had baseline mRS > 2. Seven of the 12 pts with 90 day outcome data (one patient lost to f/u) had f/u mRS $\leq$ 1 point higher than baseline mRS. Ten TM consultations were attempted during MSU weeks, and all were completed. There were no TM technical issues, except on one occasion, the TM signal was intermittent due to inclement weather. Agreement between the MSU VN and TM VN on whether or not to administer tPA was 89%. There were no technical issues with CT scanning or CT scanner performance.

4.D. Initiation of randomization and progress to date. After this run-in phase, we began randomized MSU and SM weeks on August 18, 2014. We remain blinded to data on MSU vs SM weeks since randomization began. During the first 14 MSU + 13 SM weeks, we have enrolled a total of 74 patients, and treated 45 with tPA. For planning our ability to recruit our required sample size of tPA treated patients, this equates to approximately 1.7 tPA treated patients per week overall. There have been zero TM or CT technical concerns since randomization began. We have been able to obtain informed consent in all enrolled patients, and obtain 90 day f/u in 90% of enrolled patients who have survived to 90 days. N.B. Once the MSU is deployed, we cannot pre-screen patients before enrollment for likelihood of follow up availability or for pre-stroke morbidity. Therefore, we have built a 10% lost to follow-up proportion into our sample size estimates, and assume based on our run-in data that about one third will have baseline mRS >2.

4.E. Multiple sites. The University of Colorado in Aurora, University of California in Los Angeles (UCLA), New York Presbyterian Hospital, University of Tennessee in Memphis, Mills Peninsula Hospital in Burlingame CAhave purchased their own MSUs. Their princip[illegible]iators, William Jones, MD,

May Nour MD, Michael Lerario MD, Andrei Alexandrov MD, and Joey English MD have committed to participating in this study and following this protocol, including randomization to MSU vs SM weeks. Subsequently, Indiana University was added (Jason Mackey MD). All data will be entered into the electronic database coordinated by the Data Coordinating center at the UT School of Public Health.

5. Study Design

We aim to carry out a multicenter prospective cohort study with randomized MSU or SM deployment weeks and blinded assessment of both trial entry as well as clinical outcomes. Since tPA treatment will occur at different time points in the study arms, our protocol is designed to reduce the potential for bias due to lack of allocation concealment. All potential stroke patients will be identified by a 911 dispatch center adhering to current standard of care protocols and subsequently screened for trial inclusion (confirmed neurological deficits with onset well within the IV-tPA treatment window and typical stroke mimics such as hypoglycemia excluded) at the same pre-hospital time by the same investigators on both MSU and SM weeks to ensure that comparisons are made between similar patients. Anyone transported on the MSU (or SM patients who are deemed eligible for MSU transport) will be considered as enrolled into the study and eventually consented for participation. Therefore, comparable patients in the SM group will also be enrolled and consented. For all patients enrolled, criteria for study enrollment and tPA treatment will be subsequently reviewed by a vascular neurologist blinded to MSU vs SM assignment. For comparing outcomes between MSU and SM, we will only include patients meeting criteria for tPA treatment, whether or not actually treated, based on a blinded review of prehospital information. We will report baseline comparability of clusters (patient co-morbidities, age, stroke severity), plan an intention-to-treat analysis, and will implement an aggressive protocol to reduce lost to follow-up and thus differential missing data. Finally, all 3 month mRS measurements will utilize a standardized questionnaire (Rankin Focused Assessment) which will be obtained from the patient by an investigator blinded to treatment allocation.

5.A. Inclusion Criteria

There will be three decision points for inclusion of patients into either the MSU or SM arms (see flow chart, Appendix 1): 1. Whether to call the MSU team at the time of the 911 call or EMT evaluation; 2. Whether the patient might be a tPA candidate when evaluated by the MSU team pre-hospital; 3. Whether the patient meets criteria for IV tPA treatment.

1. **Criteria to alert MSU Team (by either a, b, c, or d, and meeting all criteria i-iv):**
    - **a.** HFD, Bellaire, or West University EMS dispatch center based on caller identification of possible stroke. (Comparable alerting mechanism in Colorado, California, New York, Indiana, and Tennessee).
    - **b.** EMT or paramedic on scene recognizing a possible stroke
    - **c.** MSU team identifies a possible stroke by monitoring EMS communications
    - **d.** EMS base station calls MSU team for stroke patient en-route to one of the CSCs
        - **i.** Last seen normal on the same day as 911 call to EMS dispatch, and after awakening
        - **ii.** EMS decision to transport the patient to one of the CSCs within pre-designated “catchment area” of MSU
        - **iii.** Call to dispatch within pre-established hours of availability
        - **iv.** $\geq$ 18 years old
2. **Criteria for MSU team to enroll patient into study** (to be carried out pre-hospital)
        - **i.** Last seen normal (LSN) possibly within 4hr 30 min
        - **ii.** History and physical/neurological examination consistent with acute stroke
        - **iii.** No definite tPA exclusions per guidelines[1], prior to CT scan or baseline labs
        - **iv.** Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment, including IV tPA, will not be delayed for consent; however, consent in both MSU and SM patients must eventually be obtained for data to be retained for analysis.
3. **Criteria for tPA eligibility** (to be determined pre-hospital on MSU weeks and after ED assessment on SM weeks, and confirmed by blinded adjudication
        i. Meeting all tPA inclusion and exclusion criteria per guidelines[1] after CT scan, baseline labs, and clinical re-evaluation

5.B. Study Population

To be assessed for eligibility (n = 10000)
To be enrolled (n = 2000)
To be analyzed ("tPA eligible") (n =1038)

Based on our pilot data in the first 9 months of operation, the MSU is being alerted and dispatched by Criteria 1 above approximately 5 times for every patient that is enrolled into the study by Criteria 2, and 10 times for every patient treated with tPA by Criteria 3. Therefore, we anticipate that slightly over 50% of enrolled patients will be treated with tPA. We calculate that we will need 1038 tPA eligible patients (meeting above Criteria 1, 2 and 3) to answer SA 1 allowing for 5% lost to f/u (see Statistical Methods).

5.C. Intervention (Comparable paradigms will occur in California, Colorado, New York, Indiana, and Tennessee)

5.C.1. Integration of the trial into routine emergency medical service (EMS): All emergency 911 calls are routed automatically to the Houston, Bellaire, or West University EMS dispatch centers. Enrollment into this study currently takes place from 8 am to 6 pm, 7 days/ week. Each morning and evening, the MSU team calls the EMS dispatch centers and places the MSU team on or off call. During on-call hours, the EMS dispatch centers alerts the MSU team via dedicated pager and cell phone for all possible stroke patients (see below), but the MSU is only dispatched on 50% of the weeks. On non-MSU dispatch weeks (SM weeks), the MSU team is still dispatched but travels in a private vehicle (N.B. Neither the UT CPHS or EMS will allow us to arrive on-site with the MSU and not utilize it if the patient is having a stroke. Therefore, we cannot dispatch the MSU to the scene on SM weeks, and furthermore, we cannot exclude patients who qualify for tPA treatment on the basis of uncertainty of follow-up or pre-stroke disability). Some sites in the study, such as Houston, have two simultaneous locations, the MSU is on call in one location for the week while SM occurs the same week in the second location.

5.C.2. Notification of the MSU team. Once the MSU team notifies the dispatch center that they are on-call, 911 calls are screened for stroke symptoms by EMS dispatchers. Both the dispatchers and their supervisors have been trained in stroke symptoms by the MSU Team. Training includes an instructional DVD reviewing stroke symptoms and loaded onto their computers, and a printed algorithm of questions to be asked if stroke is suspected. Currently, all calls are immediately triaged by the dispatcher onto one of 44 diagnostic pathways such as "fall", "chest pain", "gunshot", etc. Only one of these pathways is "stroke". After listening to the initial history, the dispatcher immediately dispatches the nearest available Emergency Medical Technician (EMT) or Paramedic team depending on proximity of available units and severity level of the pathway. After EMT/paramedic dispatch, the MSU team is activated by one of four pathways (see Criteria 1, in Section 4 above). 1). If the caller mentions the word "stroke", the call is triaged onto the "stroke" pathway and if the patients is within the catchment area of the MSU (see below), the dispatcher also immediately dispatches the MSU team using a dedicated beeper and cell phone line. 2). If the patient is triaged on one of the non-stroke pathways and the MSU team is not alerted by the dispatch center, but the EMT or paramedic arrives on the scene, discovers that the patient may have had a stroke, and that one of the designated CSCs is a possible transport option, they call back to the dispatch center and ask for MSU team dispatch. All EMTs and paramedics operating within the catchment area of the MSU have been trained in stroke recognition and the need to ask for MSU team dispatch. 3). The MSU team monitors all communication between dispatch and EMS units, and if a possible stroke patient is identified, the MSU team contacts the EMS unit and ask to be "added on" to the call if one of the designated CSCs is a possible transport option. 4). All EMS units transporting stroke patients call the base station for instructions and hospital pre-notification. The base station alerts the MSU team for all transported stroke patients. This serves as a "back up" to methods 1-3. If the MSU team is notified by any of these 4 pathways for a possible stroke and the patient meets Inclusion Criteria as in section 4.1.b.i-iv, the MSU team is deployed. Depending on MSU or SM week, or location of the emergency call in the case of dual MSU/SM locations, either the MSU is dispatched, or the SM pathway, which already has been initiated, is continued.

5.C.3. Mobile Stroke Unit process: The MSU is staffed by an off-duty Houston Fire Department paramedic, certified CT technician, Vascular Neurologist (VN faculty or fellow) and research nurse (RN). In some cases, the VN is not on board and manages the case remotely via TM; in these cases, the MSU team alerts the on-call TM VN who immediately connects to the mobile TM device on the MSU. Once alerted, the MSU is driven by the paramedic with the VN riding "shotgun" and helping to navigate, while the CT tech and RN ride in the back.

The MSU is stationed in the driveway of the UT-Professional Building (UTPB) which houses the MSU team offices on the 14th floor. There is an elevator outside the MSU team office door leading to the outside door opening onto the designated MSU parking spot. The UTPB is in the heart of the Texas Medical Center (TMC), and surrounded by the 3 CSCs which are the destination of all MSU transports. Currently, direct dispatches of the MSU by EMS are limited to a 5-8 mile radius of the MSU office. We have found that this radius "catchment area" allows dispatch and arrival of the MSU at the emergency site during the time EMS is still on-scene evaluating the patient. Additionally, the MSU is alerted to patients from outside the catchment area by pathways # 2 or 3 in section 6b. Under any of these pathways, if the MSU cannot reach the patient before the EMS unit is ready to depart the scene with the patient, the MSU can arrange to "rendezvous" with the EMS squad en-route. Both the paramedic and RN carry a two-way HFD radio and establish direct radio communication with the EMS team in charge of the patient on site. This enables the MSU team to notify the on-site EMS team that they are en-route, their ETA, and, in some cases, the need to rendezvous. Also, the two way radio allows the on-site EMS squad to "disregard" the MSU if the squad determines that the patient does not have a qualifying stroke.

Once the MSU is activated and assigned to a case, they are considered "out of service" until the call is completed; during this interval they are not activated for any additional stroke alerts.

Once on scene, the patient's medical history, vital signs, finger stick glucose, and physical examination are jointly evaluated by the EMS paramedics and MSU VN and RN, and if the patient has signs and symptoms of stroke possibly within 4 hours 30 min of LSN they are moved into the MSU. This is a critical decision point (see Criteria 2, in Section 4 above). **If the patient meets all inclusion criteria except lab and CT (which have not yet been done), the patient is then <u>enrolled</u> into the study for purposes of answering the Specific Aims, and assigned to the MSU arm**. If the patient does not have signs and symptoms of a stroke, is clearly outside the 4.5 hour time window, has other definite tPA exclusions, or is clinically unstable (such as requiring pressor or ventilator support), they are managed and transported per EMS routine. These patients are considered "screen failures" and a one page CRF completed including diagnosis and reason for exclusion.

Making the tPA decision and the relative roles of the TM VN and on-board VN and MSU team: During the initial phase of the study, we validated the accuracy and speed of the TM VN evaluation in comparison to the on-board VN. The following interaction is how we have developed the workflow in order to avoid delay while at the same time allowing the TM VN and on-site VN to make totally independent decisions about tPA treatment without ever knowing the others' decision. The initial evaluation of the patient and decision whether or not to enroll the patient is made off the MSU in the patient's home, workplace etc, or in the case of a rendezvous, in the adjacent HFD ambulance, by the on-site VN. During this time, the on-site VN obtains the initial history, exam and NIHSS. Once the on-site VN decides to enroll the patient, the patient is moved into the MSU, and vital signs measured, IV access obtained, and blood samples analyzed via a point of care (POC) laboratory (blood glucose, hematocrit, INR if needed) by the RN. The on-site VN works with the RN to control blood pressure, oxygenation, glucose etc as needed. Simultaneous to these events once the patient is moved into the MSU, the TM VN evaluates the patient with the help of the paramedic, using the portable In-Touch RP-Xpress mounted at the foot of the patient's gurney or hand held by the paramedic to optimize viewing. The paramedic (and RN if necessary) communicates with the TM VN over the TM device helping the TM VN obtain the history and carry out the NIHSS, and record the vital signs and POC lab results. During the TM VN evaluation, the CT tech is positioning the patient for the CT scan. Once the RN has the IV in place, labs completed, and VS stable, and the CT tech has the patient in position, the TM consult is interrupted and a non-contrast CT scan of the head performed. The CT technician immediately uploads the data onto PACS for immediate visualization on the MSU laptop computer, and also securely and wirelessly sends it via on-board 4G connection in real time to a secure PACS system for review by the TM VN. Eventually the images are also pushed via a dicom grid to the receiving facility. While the on-site VN is reading the CT scan on the laptop (located outside the MSU so the on-site VN does not observe the remainder of the TM consult), the TM VN completes their evaluation with the assistance of the RN, and signs off, ending the TM consult. The on-site VN, after completing their review of the CT scan, and after the remote TM VN has signed off, completes their evaluation including NIHSS, and decides whether the patient qualifies for tPA ("**therapy decision time**"). **If the patient meets all inclusion and exclusion criteria for thrombolysis according to published guidelines during the pre-hospital evaluation by EMS and the MSU team, then the patient is considered a "MSU tPA-eligible patient"**, whether or not they eventually receive [illegible] e MSU (for instance, there

may be a problem with IV access or some other technical failure on board). The IV tPA bolus is given without delay **("tPA needle time")**, followed by the infusion. If after seeing the labs, CT scan, vital signs and neurological exam, the on-site VN thinks that the patient does not qualify, tPA is deferred. The ultimate decision whether or not to give tPA is made by the on-site VN, without knowledge of the TM VN decision. In patients who may be candidates for endovascular therapy, a CT angiogram (CTA) may be carried out to determine the optimal hospital destination (primary vs comprehensive stroke center).

Once the TM study showed acceptable reliability and accuracy of remote TM assessment, we allow replacement of the on-board VN with remote VN TM assessment for blocks of time. Our analysis plan will evaluate any interaction of remote TM vs on-site VN subgoups and outcomes (see Analysis section).

After tPA is initiated, or the decision made to withhold tPA, the patient is then transported in the MSU with RN and VN to the appropriate CSC (the paramedic drives with the CT tech riding in the front). Patients receive standard EMS routine pre-hospital stroke care en-route, and if treated with tPA also receive standard post-tPA monitoring (q15 min VS, neuro checks and observation for angioedema). Destination hospitals include any of the certified CSCs within the 5 mile radius catchment area of the TMC, and are selected by EMS according to their usual criteria. The destination hospital and their stroke team are pre-notified by the MSU team, and all further care carried out at the destination ED according to their usual routine. The RN or VN obtain consent, and visit the patient on days 0-3 at the hospital and day 90 in clinic or at home, and record study related data on the CRF.

If a stroke alert is called while the MSU is "out of service" because they are occupied on a simultaneous call or for mechanical/maintenance issues, the patient may still be eligible for inclusion into the SM group if there is a second SM team on call covering the geographic area where the stroke occurs (see below). If a SM team is not available to assess the patient, the patient is not included in the study, but the reason for the "missed" patient is recorded.

5.C.4. Standard management: The MSU is not dispatched, but the MSU RN or VN is dispatched by car to the scene or meets the patient and EMS squad at the destination ED. The destination CSC is determined by EMS (these are the same complement of hospitals served by the MSU) and the hospital stroke team is pre-notified by EMS. Once on scene or at the ED, the patient's history, time last seen normal, vital signs, finger stick glucose, and physical examination are obtained from the EMS paramedics by the MSU VN or RN who then carry out their own NIHSS without delaying the EMS evaluation, transport or ED intake process, **If the patient meets all inclusion criteria except lab and CT (which have not yet been done), the patient is then <u>enrolled</u> into the study for purposes of answering the Specific Aims, and assigned to the SM arm**. If the patient does not have signs and symptoms of a stroke, is clearly outside the 4.5 hour time window, has other definite tPA exclusions, or is clinically unstable (such as requiring pressor or ventilator support), they are not enrolled and are managed per EMS and ED routine. These patients are considered "screen failures" and a one page CRF completed including diagnosis and reason for exclusion. Following the decision to enroll the patient, the MSU VN or RN then decide if the patient meets criteria for tPA. **If the patient meets all inclusion and exclusion criteria for thrombolysis according to published guidelines during the pre-hospital evaluation by EMS and the MSU team, and if the baseline labs and CT scan obtained once the patient reaches the ED do not exclude the patient, then the patient is considered a "SM tPA-eligible patient"**, whether or not they eventually receive tPA in the ED (for instance, the 4.5 hour time window might be exceeded, or the patient's deficit might have resolved, by the time the patient is fully evaluated in the ED).

The hospital based stroke team manages the patient as per stroke center routine and the same standard of care analyses carried out as with the MSU treatment. IV tPA is given as per the hospital based stroke team. If the patient does receive tPA in the ED, the "**therapy decision time**", and **"tPA needle time"** are recorded. For all SM enrolled patients, whether or not they actually receive tPA, the RN or VN obtain consent, and visit the patient on days 0-3 at the hospital and day 90 in clinic or at home, and record study related data on the CRF.

TM is not carried out on SM weeks.

5.D. Blinded adjudication: All enrolled patients are reviewed by a VN blinded to assignment of MSU vs SM management and not involved with either MSU or remote TM patient management. The blinded VN determines from a dedicated "adjudication form" that is missing any time data or other information that would produce unblinding, if the patient meets criteria for study enrollment and for tPA treatment. If the patient is enrolled or considered to be a "tPA-eligi" by either the MSU or SM

enrolling team, but do not meet criteria after adjudication, they will not be included in data analysis of the primary outcome. If an enrolled patient meets criteria for tPA but is not treated, that fact will be noted, the patient considered a "miss", and the patient will still be followed and outcomes measured. For comparing the primary outcomes between MSU and SM, we will only include tPA-eligible patients in both the MSU and SM groups, whether or not actually treated, based on this blinded review.

5.E. BP: On both MSU and SM weeks, blood pressure is measured at baseline and thereafter according to EMS routine, and treated to target levels, according to published guidelines for ischemic stroke, pre and post-tPA treatment, and for intracerebral hemorrhage. The time of first BP treatment is recorded.

5.F. CT: A cerebral CT scan must be performed on all patients meeting Inclusion Criteria for IV tPA, and the CT scan must be read by the MSU VN prior to the initiation of tPA treatment. Follow up CT or MRI imaging is optional as is the timing. It is carried out as per routine care and results recorded if done. CT or MRI are immediately performed in the case of neurological deterioration.

5.G. TM: The TM connection is Health Insurance Portability and Accountability Act (HIPAA) compliant and encrypted. VNs connect to the device from a desktop computer. Connections are encrypted using a combination of RSA public/private key and 256-bit advanced encryption standard symmetrical encryption to ensure confidentiality of patient information transmitted.

5.H. Informed consent (Appendix 2). Informed consent is obtained at any time during this process by the MSU team VN or RN from either the patient (if competent) or legal representative. In no case is standard of care, including CT scanning and tPA administration whether in the MSU or hospital, delayed in order to get informed consent. This study only involves standard of care management of stroke patients according to current guidelines, and patients are managed in the MSU by personnel with the same training and expertise as they would receive in the CSC stroke center ED, and costs to the patient for their pre-hospital and ED care are the same whether they are managed on the MSU or SM pathway. **According to current HFD EMS policy, all acute stroke patients within the catchment area of the MSU are transported to the same CSCs that receive MSU patients so that the study does not involve "re-routing" of patients**. Specifically regarding costs, patients are charged the same technical fee for CT scanning, tPA and other medications whether administered in the MSU or ED, and pre-hospital transport is billed the same whether by MSU or SM. The CT reading professional fee is also the same whether the CT is carried out in the MSU or ED. Regarding risks, there is no evidence that a CT scan and other diagnostic procedures performed in the same way as in the hospital, but at the site where the patient is found, is less effective or has more complications than in a hospital. A CT scan is performed whether the patient is in the study or not to determine diagnosis of a stroke. The CT scan exposes patients to a small amount of radiation, (about 1.02 cGY). Since CT scanning, tPA administration, and all other pre-hospital procedures in this protocol **including choice of destination hospital** are standard of care and follow published guidelines, The UT Committee for the Protection of Human Subjects has ruled that informed consent is not required prior to their performance. Informed consent is needed to include patient data for this study. Consent is usually not obtained until the standard of care acute stroke patient care process is complete and the patient and/or legal authorized representative has adequate opportunity to review the informed consent document. Data recorded by the research nurse will be discarded if consent is not obtained. If the patient refuses to participate, this will not have any influence on either diagnostic or therapeutic procedures. We have considered exception from informed consent, but a very low percentage of our patients have both decreased consciousness/inability to communicate or no legal relative. To date, we have been able to obtain consent on almost 100% of our enrolled patients.

5.I. Concomitant therapy. All treatments are given according to standard of care protocols or published guidelines. Off-protocol unapproved treatments are not allowed. The use of intra-arterial thrombectomy (IAT) is allowed in this study but follows published guidelines, e.g. patients with carotid T, M1, A1, proximal M2, or basilar occlusions on screening vascular studies, and groin puncture within 6 hours (4 hours prior to 2/16/15) of symptom onset following curent guidelines[18] (see Appendix 3). To date, about 17% of MSU tPA treated patients have received IAT. Although this number is relatively small, we recognize the possibility of "collider bias" in interpreting MSU vs SM results in the subgroup of patients undergoing IAT (see Potential Biases section 13). Conceivably, MSU pts will need less IAT if they respond to earlier tPA, or, if they need IAT, MSU pts may get it faster due to earlier warning, so that better outcomes in those patients may be due to earlier IAT and not directly due to earlier tPA treatment. Also, benefit from IAT in SM patients may obscure the positive effect of the MSU intervention. While these considerations may confound interpretation of results, they should not

prevent us from determining if MSU has a beneficial effect if added to background therapy. Considering that IAT is now considered background therapy, the main impact of IAT will be on the expected 90 day mRS and therefore the power/sample size. A sensitivity analysis will be carried out both including and excluding patients receiving IAT.

5.J. Recruitment and Retention Plan. We calculate that we will be able to recruit enough patients to answer the Specific Aims. We already implemented our first recruitment stimulus by arranging to rendezvous with EMS units bringing stroke patients to the Texas Medical Center (TMC) from beyond our 5-10 mile (radius) catchment area. Transport of some patients to the CSCs from beyond 5-10 miles and paramedic rendezvous are already part of routine EMS practice policy and does not involve "re-routing" of patients for this study.

Another strategy to increase recruitment was to identify a second location for the MSU in a Southwest Houston. The MSU vs SM weeks at this second location would complement the SM and MSU weeks of the unit when it is located at the TMC so that the MSU will constantly be enrolling patients, either at the TMC or the southwest location. The southwest location has a high stroke incidence with large Hispanic and Asian population only partly overlapping in catchment with our currrent TMC location.

A key to successful recruitment rests with the enthusiasm of EMS, a major stakeholder in this study (including EMTs, paramedics and dispatchers) to engage in the project. To date, the MSU team has made 40 visits to HFD Fire Stations to meet individually with the EMTs and Paramedics who alert us to stroke patients and work with us in the pre-hospital environment. Also, we have in-serviced 696 dispatchers and their supervisors. To maintain enthusiasm, we send twitter and facebook messages recognizing the EMS units that alert us to a patient we enroll. Such positive feedback to EMS (though there was no social media) was very successful during the NINDS tPA Stroke Study, and EMS personnel often remind us of certificates of recognition they received years ago. EMS representatives have been incorporated into the study design, conduct, and dissemination of results.

Finally, we will increase the number of MSUs participating in the study. Dr Andrei Alexandrov at the University of Tennessee in Memphis, Dr William Jones at the University of Colorado in Denver, Dr. Mackenzie Lerario at New York Presbyterian/Cornell, Dr. May Nour at the University of California in Los Angeles, and Dr Joey English at Mills Peninsula Hospital in Burlingame CA, and more recently Jason Mackey at Indiana University have all obtained local funding to purchase, staff and equip a MSU,obtained IRB approval and are now enrolling patients. Dr Grotta has collaborated with all of these teams in the past, and made site visits to each location vetting their research capability, availablility of patients and cooperative EMS partners, patient and EMS engagement, and commitment to alternating weeks. The Colorado site utilizes two locations, one in Aurora and one in Colorado Springs, rotating their MSU and SM weeks betwween the two locations. Recruitment projections are included in the timeline. These sites will provide power to answer our Specific Aims, and increase the generalizability of our results. Note that the procedures outlined in this Research Strategy will be employed at all participating sites.

In summary, as outlined in the milestones table, we are enrolling 70+ tPA-eligible patients per year with one MSU in Houston operating 8am-6pm, or a total of 150+ patients over the first 2 years of enrollment prior to start of PCORI funding. Conservatively, we expect to enroll 90+ per year X the next 3 years of enrollment by having the MSU available in a second location. By also adding the other sites named above, we should easily be able to reach our target of 693 tPA-eligible patients by the end of 5 years of recruitment.

We maintain an aggressive program to prevent patients lost-to-follow up. Since the intervention our team is conducting in this trial requires our leaving the medical center to treat patients all over the city, doing the same to obtain follow up in case the patient cannot return to the medical center is not a break from routine operations in this study. Routine follow-up data collection starts a week before the "due date" (the date on the 3rd, 6th, 9th and 12th month after the patient has been discharged) up to a week after. The patient is called every day to schedule the follow up visit either at our clinic, or wherever the patient is residing, and a voice-mail message is left if the patient does not answer. If we are unable to reach the patient directly, the patients' emergency contacts are then called and calls intensified until a month after the due date. If we still are unable to reach the patient, we will do a "drop-by" house call unless the patient is homeless or moved to a different city. If necessary, the follow-up visit is made by telephone. After each contact, the patient is re-informed about the importance of follow-up for the entire year, reminded to be on the lookout for a call in a few months, and reaffirms the best phone number for subsequent follow-up. To date, of all tPA-[redacted]atients during run-in and

randomization who have survived to 90 d, we have obtained outcome data on over 90%. N.B. Once the MSU is deployed, we cannot pre-screen patients before enrollment for likelihood of follow up availability. Therefore, we initially built a 10% lost to follow-up into our sample size estimates, but reduced this to 5% based on our first two years' experience.

5.K. Representativeness of participants, subgroups, and engagement of stakeholders. Patients are included if they call 911 between 8 am and 6 pm, and are located within our catchment area; and they are enrolled regardless of their insurance, race/ethnicicty, socioeconomic, or disability status (unless they have a baseline mRS of 5= bedridden and totally dependent). The following vulnerable populations are represented in our study: adults, especially > 80 years old (we will only enroll patients over 18 years old because tPA is not approved for use in children, and most stroke patients are elderly), disabled persons, racial and ethnic minorities, residents of urban areas, women, low income groups, patients with low health literacy and English proficiency, and individuals with multiple chronic conditions (such as hypertension and diabetes). Stroke is more prevalent and with worse outcome in African American and Hispanic patients who are also underserved from the health care perspective[2]. Furthermore, patients in these groups have the highest rates of 911 activation. Therefore, we expect that they will continue to be highly represented in our data, and we have and will continue to reinforce our efforts to recruit them. In our pilot data, 32% of patients enrolled were > 80 yo, and remains at approximately 25% in our overall randomized database to date. In our pilot data, 55% of patients enrolled were African American and 21% Hispanic (44% and 16% in our overall randomized database to date). Our MSU crew includes at least one African American, and one Spanish-speaking member on each shift. A unique and important aspect of our study is to include patients with baseline disability since stroke is common in this population. They may benefit from new therapies or interventions such as MSU management, but have not been included in previous acute stroke studies which have had recovery to no disability as their primary outcome. In our pilot data, 34% of patients enrolled had a baseline mRS $\geq$ 2 (29% in our overall randomized database to date). In our pilot and randomized data, 50% of enrolled patients are women. Because of the catchment area of our study and the projected expansion to other sites, we expect an increase in Hispanic and Asian patients because of their proximity to the projected second hospital location in Houston, and African Americans because of their high prevalence in Memphis and our primary Houston site. These communities are represented in our patient advisory committee and, as will be described, we maintain an active outreach program to the communities we service, in particular the underserved and low socioeconomic African American community in central and south Houston.

5.L. Avoiding bias. We aim to carry out a prospective randomized cluster trial with MSU or SM deployment weeks and blinded assessment of both trial entry as well as clinical outcomes. The ideal study design to test efficacy of MSU vs. SM stroke treatment would be a randomized clinical trial with patient as the unit of randomization. In the latter design, treatment assignment (MSU or SM pathway) would happen in a randomized fashion either at the time of 911 call or after arrival on-scene when many stroke mimics or false-alarms can be ruled out. However in both these scenarios, the MSU would need to be available and deployed on each and every possible stroke call. Unfortunately, this design is not feasible since we have only a single MSU and staffing the unit 7 days a week every week has been cost-prohibitive to date. Also, on SM weeks neither the UT CPHS nor EMS will allow us to arrive on-site with the MSU and not utilize it if the patient is having a stroke. Therefore, on non-MSU dispatch weeks (SM weeks), the MSU team is still dispatched but travels in a private vehicle.

A valid criticism of such a cluster randomized trial is that bias can be introduced through differential recruitment across treatment groups. We have introduced several design features into our pragmatic study to reduce the potential for bias due to lack of allocation concealment. All potential stroke patients will be identified by a 911 dispatch center adhering to current standard of care protocols. All patients will be subsequently screened for trial enrollment at the same pre-hospital time by the same investigators on both MSU and SM weeks to ensure that comparisons are made between similar patients.

For all patients enrolled, criteria for study enrollment and tPA treatment will be subsequently reviewed by a VN blinded to MSU vs SM assignment and not otherwise involved in study management or analysis. The blinded VN determines from a dedicated "adjudication form", omitting any time data or other information that would produce unblinding, if the patient meets criteria for study enrollment and for tPA treatment. If the patient is enrolled or considered a "tPA-eligible patient" on either MSU or SM weeks, but do not meet criteria after adjudication, they will not be included in data analysis of the primary outcome. If an enrolled patient meets criteria for tPA after [redacted] on, but is not treated, that

fact will be noted, the patient considered a “miss”, and the patient will still be followed and outcomes measured. For comparing outcomes between MSU and SM, we will only include tPA-eligible patients, whether or not actually treated, based on this blinded review.

We will report baseline comparability of clusters (patient co-morbidities, age, stroke severity), plan an intention-to-treat analysis, and will implement an aggressive protocol to reduce lost to follow-up and thus differential missing data. Finally, all 3 month mRS measurements will utilize a standardized questionnaire (Rankin Focused Assessment) which will be obtained from the patient by an investigator blinded to treatment allocation.

Another bias might be introduced by the confounding effects of concommitant therapies such as endovascular treatment (IAT). We will try to achieve standardized management by only admitting patients to a certified stroke center and VN service, by direct discussion of expected management between the VN team and the MSU team at the time of admission, by feedback from our RN who will be visiting the patients regularly during the first few days, and by asking these teams to adhere to published guidelines for stroke management[1,19]. Regarding IAT, recent clinical trials of IAT[14-17] have shown striking and consistent benefit in patients with severe strokes (median NIHSS 17, IQ 12-21), who have persisting large artery occlusion in the anterior circulation after receiving IV tPA, have small core infarcts on CT scan, were treated with the latest stentrievers, and had groin puncture at ~3.5-4 hours post onset. To date, 17% of our MSU tPA treated patients have received IAT, all of whom met criteria for IAT following criteria in recently published guidelines for IAT[19]. We expect that this percent will increase somewhat as clinical practice responds to additional data from these trials. All CSCs participating in this study will offer IAT according to published guidelines[19], and as new data become available and incorporated into guidelines, we will incorporate them into the BEST-MSU trial. Shortening the time from LSN to start of IAT may be an important advantage to the MSU. However, we recognize that earlier treatment on the MSU might lead to more tPA success and therefore fewer IAT treatments in the MSU arm. Conversely, MSU management might increase the use of IAT by allowing more patients to be treated within the time window of possible IAT efficacy. Finally, SM patients may benefit from IAT obscuring some of the benefit of the MSU intervention. Since patients managed by either MSU or SM will have comparable access to IAT, any difference in the frequency of IAT between the arms would be a consequence of the effect of MSU vs SM management, and therefore will be important to measure and factor into our analysis. However, we will not be able to adjust for post-intervention IAT management, but rather need to consider it as part of “background therapy“ in this trial that compares MSU + background therapy to SM + background therapy. To explore any confounding effect, we will present descriptive statistics of IAT treatment in both arms and conduct sensitivity analyses, including a time-dependent covariate for IAT in the Cox model for mortality, using propensity score anlaysis of who received IAT in the analysis of 90-day mRS, and subset analyses including/excluding IAT patients.

5.M. Assuring protocol adherence. (See Figure 1, data collected). Direct data collection begins at time of screening and continues until it is determined that the subject is not eligible, the patient or family refuses consent, or the patient drops out or completes the study. Data on eligibility are submitted to the Data Coordinating Center (DCC) to allow description of screened versus enrolled subjects. The DCC will complete analyses of data quality including missing data, error patterns, protocol violations, etc. to determine if modifications in the protocol or data collection procedures or trial manual of operations are needed. The Study Monitoring Committee will review blinded data on recruitment, protocol deviations, data quality and adherence to study procedures, including a count of the number of instances when patients were not randomized.

We will take several steps to assure standardized data collection and outcome assessment across centers. These include a site initiation visit and yearly site visits from the Clinical Coordinating Center (CCC) and DCC and weekly phone calls from the CCC to each site Operating Committee (sOC). The initiation visit will include training on the protocol and outcome measures including the Rankin Focused Assessment for assigning mRS values. We will share our Manual of Operations which provides details on completing the Case Report Forms. Data from each site will be edited by the DCC for consistent patterns (digit preference, etc) that might suggest that recorded data are not accurate. The research nurse at each site will monitor all data for completeness and accuracy by comparing with source documents.

6. Outcomes for Specific Aims

6.A. Outcomes for S.A. 1 (in hierarchical sequence of importance).

6.A.1. Primary Outcome. Mean Utility-weighted mRS at 90 days, comparing patients found eligible for tPA (intention-to-treat based on a blinded review of the patient's chart, regardless of whether they were treated or not) onMSUweeks compared to SM weeks.

Virtually all acute stroke treatment trials carried out in the past decade, including the NINDS tPA study and the recent positive IAT studies[3,14-17], utilize as primary outcome the Modified Rankin Score (mRS), a 7 point scale (ranging from 0=normal to 6=dead) where the physician assigns the score based on the patients' observed and reported level of disability. A standardized questionnaire has been developed to help reduce variability in assigning mRS values. The most widely accepted patient centered outcome measure is utility - the desirability of a specific health outcome to the patient[32]. For this trial, we will use a patient-centered adaptation of the mRS, the utility-weighted mRS (uw-mRS), as our primary outcome measure for SA-1. The uw-mRS assigns values to each mRS grade depending on patients' value of that level of function, with lower mRS scores (reflecting less disability) given proportionately higher weight than higher mRS scores (reflecting more disability)[20]. Utility weights for each level of the mRS were derived by averaging utility values obtained from patients with TIAs or strokes and using methodology of the World Health Organization Global Burden of Disease Project. Furthermore, a substantial number of stroke patients (roughly 30% in our preliminary data) who qualify for tPA treatment on the MSU have pre-existing disabilities (baseline mRS $\geq$2) making it impossible for them to achieve a non-disabled mRS outcome (mRS 0 or 1). For this reason, disabled patients have traditionally been excluded from acute stroke treatment trials which have defined success as achieving a mRS of 0 or 1. We will include patients with pre-existing disability; thus the uw-mRS will consider patients who begin with disability to have a favorable outcome if their stroke and its treatment results in an overall improved mean uw-mRS score. In a re-analysis of 11 acute stroke studies, the difference in mean 90d uw-mRS between groups ranged from 0.024-0.25, with most trials in the range of 0.1. For instance, 90d mean uw-mRS was 0.59 vs 0.50 with tPA vs placebo in the NINDS tPA trials[20].

6.A.2. a. Mean utility-weighted mRS at 90 days,
b. ordinal (shift) analysis of mRS at 90 days, and
c. proportion of patients achieving 90 day mRS 0,1 vs 2-6

of enrolled patients treated with tPA within 60 minutes of LSN onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS) between the groups at the time of treatment. **N.B**. Patients will include only those patients actually treated with tPA based on the final determination of the time LSN, and will include only patients meeting all inclusion and exclusion criteria.

6.A.3. a. ordinal (shift) analysis of mRS at 90 days, and
b. proportion of patients achieving 90 day mRS 0,1 vs 2-6

comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to SM weeks.

6.A.4. The time from LSN to tPA treatment on all patients treated within 4.5 hours of LSN on MSU weeks compared to similarly eligible patients on SM weeks. **N.B**. Patients will include all enrolled patients actually treated with tPA (or on SM weeks, eligible for tPA treatment) meeting all inclusion and exclusion criteria, and based on the final determination of time of LSN. One analysis will compare the median times. A second analysis will also capture the patients who were eligible but did not receive tPA because it was too late, categorizing time into the following groups (e.g., 0-60min, 61-90min, 91min-180min, 181-270min, eligible but no tmt because>270).

6.A.5. Of the enrolled patients that were eligible for treatment with tPA (according to published guidelines) on MSU compared to SM weeks, the percent that were treated within 4.5 hours and within 60 minutes of LSN.

6.A.6. The time from LSN and from ED arrival to start of endovascular procedure (intra-arterial thrombectomy-IAT) in patients who meet pre-specified criteria for IAT on MSU weeks compared to SM weeks. **N.B.** All patients receiving IAT will be included in this outcome.

6.A.7. The median/mean time from LSN to tPA therapy decision on all patients considered for treatment within 4.5 hours of LSN on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patients meeting inclusion criteria whether or not treated with tPA.

6.A.8. Time between 911 call and onset of etiology-specific BP management on MSU weeks compared to SM weeks. **N.B.** Patients will include all enrolled patie

6.B. Safety Outcomes for S.A. 1

6.B.1. The incidence of symptomatic intracranial hemorrhage (sICH) in enrolled tPA treated patients on MSU weeks compared to SM weeks (Symptomatic intracranial hemorrhage defined as any intracranial blood accumulation associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration) **N.B.** Patients will include all patients treated with tPA, whether or not they meet all inclusion and exclusion criteria.

6.B.2. Mortality. **N.B.** All enrolled patients signing informed consent will be included in this endpoint and followed until 1 year.

6.B.3. The incidence of stroke mimics and transient ischemic attacks (TIAs) in tPA treated patients on MSU weeks compared to SM weeks. **N.B**. SM patients deemed eligible for tPA on their pre-hospital assessment who then completely recover by the time of arrival in the ED will equal the excess incidence of TIAs treated on the MSU pathway.

6.C. Outcomes for S.A. 2.

6.C.1.The agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU. **N.B**. Patients will include all enrolled patients on MSU weeks considered for tPA treatment. .

6.C.2. Frequency and causes of incomplete or failed TM consultations.

6.D. Outcome for SA 3.

6.D.1. Determine health care utilization and QoL during the first year after the stroke on MSU vs SM weeks.

Stroke has a permanent impact on the patient's quality of life (QoL), thereby necessitating the use of a patient-centered effectiveness measure that considers both the quality and quantity of a patient's life, and is not limited to physician reported clinical measures or survival. Unlike most other QoL measures, EQ-5D captures both the subjective and objective aspect of a person's QoL because the instrument has an objective survey that measures the patient's basic mental health and ability to perform activities of daily living, and a subjective component where the patient chooses his/her feeling of well-being from a visual analog scale. EQ-5D and healthcare utilization data will be collected quarterly for 1 year after being discharged following the stroke hospitalization. Other outcomes to be measured in SA-3 include hospitalizations, stays in long-term acute care hospital, inpatient rehabilitation facility, skilled nursing facility, intermediate care nursing home and hospice care, and survival in MSU vs SM patients who meet criteria for tPA treatment. Outcomes for SA 3 will answer the following question important to patients, caregivers and stakeholders: Does the MSU reduce post-stroke healthcare utilization, which could be considerably burdensome physically, mentally and financially for the patient? Reduction of post-stroke healthcare utilization will also be important to healthcare providers/payers who must provide/pay for these utilizations.

7. Statistical Plan

7.A. Baseline Analyses. Although the random enrollment of participants to the two treatment arms and blinded review of tPA eligibility should ensure comparability with respect to known and unknown variables, imbalance may occur by chance. Descriptive statistics for baseline characteristics known or suspected to be associated with outcomes will be prepared for the two treatment groups for all randomized as well as all deemed "eligible for tPA" based on the blinded review. Chi-square statistics and Wilcoxon rank sum tests will be used to evaluate baseline differences between the arms for categorical and continuous variables, respectively. Any variables with baseline differences will be included in secondary adjusted analyses. Also, completers will be compared to non-completers (loss to follow-up for 90 mRS) on these baseline variables to indicate whether missingness may be considered random.

7.B. Primary Outcome Analysis. The mean uw-mRS at 90d along with corresponding two-sided 95% confidence intervals will be compared between groups using a two-sample t-test or Wilcoxon rank sum test if the assumption of normality does not hold. The analyses of uw-mRS will be adjusted for any baseline covariates that were significantly different between the two groups and covariates known to be associated with mRS, including baseline NIHSS, age, pre-morbid mRS, and previous TIA/stroke, in a linear regression model. Sensitivity analyses of the primary outcome will be conducted including ordinal (shift) analysis, and proportion achieving a dichotomized outcome of mRS 0,1 vs 2-6 using proportional odds and binary logistic regression respectively.

7.C. Secondary Outcomes Analyses. We will also compare mRS at 90d (mean uw-mRS, ordinal (shift) analysis, and proportion achieving 0,1) in tPA treated patients treated within 60 minutes of LSN to patients treated 61-270 minutes, regardless of whether they were on MSU or SM weeks. Patients (MSU vs SM) will also be compared for differences in (a) the time from LSN to tPA treatment, (b) time from LSN and ED arrival to start of IAT, and for safety outcomes (i) mortality, (ii) symptomatic intracerebral hemorrhage, and (iii) incidence of tPA treated stroke mimics and transient ischemic attacks.

A logistic regression model will be used to compare 90 day mRS 0,1 vs 2-6 of patients treated with tPA within 60 minutes of symptom onset to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS, age, premorbid mRS, and previous stroke/TIA incidence) between the groups at the time of treatment[34]. If baseline characteristics are significantly different between the two non-randomized groups, we will use propensity score analysis to limit potential bias. Also, we expect a higher incidence of spontaneous recovery (TIA) and stroke mimics may occur with earlier observation in the 0-60 minute group compared to those seen 61-270 minutes. The "natural history" of the incidence of spontaneous recovery and stroke mimics will be estimated from patients enrolled into the SM group, and will be considered in analyzing the comparison between patients treated with tPA within 0-60 min vs 61-270 min. Time to treatment and to endovascular procedures will be analyzed using Cox proportional hazards models, similarly to survival. Categorical outcomes will be analyzed using Fisher's exact test.

Unless there is sufficient power (predetermined before the analysis is begun) the approach to ancillary analysis will generally be the calculation of confidence limits on intervention group differences rather than formal tests of significance as the trial may not have high power to detect difference in all of these outcomes. However, these comparisons will add to the knowledge of the benefits and risks of the intervention.

7.D. Sample Size Justification*.* The power of this trial was evaluated based on the difference in the primary outcome, mean uw-mRS at 90 days. Based on preliminary data, we expected that 1.8 times as many MSU patients will be enrolled than SM patients due to a greater propensity of first responders to alert the MSU team on MSU weeks compared to SM weeks. With a sample size of **693 total tPA-eligible patients** (446 MSU and 247 SM patients, assuming 10% lost to follow-up), the study will have 80% power with a 0.05 Type I error rate to detect a difference between groups of 0.09 in the mean Δ uw-mRS using a two-sample t-test. This difference is plausible and important. In 90 patients randomized in our pilot study comparing a combination of Argatroban + tPA to standard tPA treatment, 90 d mean+s.d. uw-mRS was 0.59+ 0.35 with the combination vs 0.49+ 0.37 with tPA alone (a difference of 0.1), slightly greater than the difference we project. In a re-analysis of 11 other acute stroke studies, the difference in mean 90d uw-mRS between groups ranged from 0.024-0.25, with most trials in the range of 0.1. We initially based our effect size on the NINDS tPA trial. In that study, 90d mean uw-mRS was 0.09 (0.59 vs 0.50) with tPA vs placebo; tPA was considered a "breakthrough" therapy based on this result. A sample size of 563 and 878 would be needed to detect a difference of 0.1 and 0.08 respectively.

Revised sample size justification. Since submitting the PCORI application, new information has emerged to suggest that a difference of 0.09 is too ambitious (Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017 Jul;48(7):2007-2012). Only the most powerful endovascular therapy trials had a difference that equaled or exceeded 0.09 on the mean uw-mRS. Positive studies such as IST 3, PROACT, and the least robust endovascular studies achieved a difference of 0.04-0.08. Finally, and most importantly, the Berlin group has published a comparison of outcomes in their non-randomized comparison of MSU treated patients vs those treated in the ED (Kunz A, et al: Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. Lancet Neurol 2016;15:1035-43). Converting their data to mean uw-mRS, they found a significant difference of 0.07 in favor of MSU management. **Therefore, we conclude that a 0.07 difference between groups (rather than 0.09 as originally proposed) is the appropriate difference to power our study.** Given the current better numerical balance between the MSU and SM patients than in our initial sample size estimates, and the current lost to follow up rate of < 5%, we conservatively calculate that 1038 total tPA eligible patients would be needed (assuming 5% lost to follow up and 1.5 imbalance) to detect a difference of 0.07 in the uw-mRS.

7.E. Interim Analyses. Interim analyses for safety (symptomatic hemorrhage), efficacy/futility (dichotomized mRS 0-1 vs. 2-6), and process (time from alarm to treatment decision) will be

conducted when the 90-day mRS has been collected on 50% of the total number of patients that are adjudicated to be tPA-eligible.

Rates of symptomatic hemorrhage will be compared using a Fisher's exact test (alpha=0.05). The futility analysis of the 90 day dichotomized mRS (0-1 vs 2-6) will be a 2-sample, 1-sided, test of proportions. The futility analysis will compare patients in MSU vs SM weeks (alpha=0.15). If we reject the null hypothesis that the percentage of favorable outcomes (mRS<2) in MSU patients is greater than or equal to the percentage of favorable outcomes in SM patients plus 10%, we conclude that completing the trial would likely be futile. The futility hypotheses are: $H_0: p_{MSU} - p_{SM} \geq \Delta$ versus $H_A: p_{MSU} - p_{SM} < \Delta$ where p_{MSU} and p_{SM} are the proportions of participants expected to have a favorable mRS outcome in the MSU and SM groups, respectively, and Δ denotes the 10% increase in favorable outcomes over SM considered clinically meaningful. The efficacy interim analysis of the 90 day dichotomized mRS will be a 2-sample, 2-sided test of proportions and will be monitored using an O'Brien-Fleming boundary with Lan-DeMets alpha spending function[35,36]. Time from alarm to treatment decision will be compared using a one-sided Wilcoxon rank sum test (alpha=0.05) to test if the time is longer for the MSU arm.

7.F. Heterogeneity of Treatment Effects. Tests of effects within subgroups will be driven by clinical rationale. To reduce the potential for spurious results, we would test for a sub-group treatment interaction at a 0.2 critical level. Any subgroup analyses that are not pre-specified would be considered post hoc and reported as requiring confirmation in future studies. Estimates of the MSU effect will be obtained separately for pre-specified subgroups with significant treatment-by-subgroup interactions, using the methods described above. Pre-specified subgroups include (1) patients treated via TM versus on-site VN, and (2) patients treated at various sites.

Analyses of post-randomization sub-groups are subject to many biases. Thus any analyses of post-randomization sub-groups, such as those treated with IAT, would be considered on a case by case basis requiring tailored use of advanced statistical methods[37] and careful interpretation.

7.G. Missing Data. We expect no missing data for baseline measures. For 90-day assessments, extensive efforts will be made to ascertain the modified Rankin scores and mortality status, though we anticipate a 10% rate of lost to follow-up. We will perform several approaches for handling missing data. Characteristics of patients who are lost to follow-up will be compared to those that remain in the study to assess the degree of any selection bias, and sensitivity analyses will be performed to evaluate robustness of conclusions to the different missing data approaches. We will use multiple imputation for the final values assuming missing at random, depending on if any significant baseline differences exist between those observations that have a missing value or not. As sensitivity analyses we will report the data with and without imputation. Data will also be stratified according to their missing pattern (e.g., early termination, late termination, and follow-up completers) and variables representing these groups will be used as model covariates in adjusted analyses.

7.H. Analysis Plan for Outcome S.A. 2: Determine the agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation. We consider the on-site VN as the "gold standard". Therefore, in determining if the remote VN can accurately replace the on-site VN, we will first test how often the on-site VN disagrees with the remote TM VN's independent assessment of whether the patient should be treated with tPA. Second, if we eventually hope to have all physicians' assessments on the MSU carried out solely by a remote VN using TM, we need to understand the variability inherent in assessing acute stroke patients for tPA on a MSU using this technology. An estimate of inter-remote VN agreement is challenging to ascertain due to ethical considerations of having another TM VN conduct an additional examination and thus possibly delay treatment. Therefore we will get an estimate of this variability by having a second TM VN review the video recording of the initial TM consultation, blinded to the final determination of the initial TM, to independently decide whether the patient should be eligible for tPA. The kappa between these two observers and the agreement between the second TM VN and the on-site VN will be tested using the Kappa statistic.

7.H.1. Sample Size: The agreement between a VN remotely assessing a suspected stroke patient via TM in the MSU and in-person assessment by a VN in the MSU will be assessed by using the Kappa statistic. **We anticipate that an estimated sample size of 162 is needed to allow us 90 % power to detect 90% agreement between the in-person assessment and the TM.**

We will also identify and calculate the frequency of TM "failures" due to technical issues such as connectivity, CT scan access or image quality, ability to obtain sufficient history, adequate clinical exam, laboratory values, or other clinical information, and non-availability, etc. See TM CRF.

7.I. Analysis plan for SA 3:

7.I.1. Approach and Methods used in analysis. Does the MSU reduce post-stroke healthcare utilization for the healthcare payers? Reduction of post-stroke healthcare utilization will subsequently save costs for the healthcare payers who pay for these utilizations.

7.I.2. Sample used: All enrolled patients on MSU and SM weeks who meet criteria for tPA treatment whether or not they are eventually treated with tPA. We estimate that approximately 50% of enrolled patients will receive tPA in the MSU and SM group. The non-tPA treated patients will probably not benefit much from MSU management and since the primary goal of the MSU is to ensure quicker administration of tPA, only those patients who meet criteria to receive tPA will be included.

7.I.3. Outcome analyses for SA 3

7.I.3.a. Data Collection:. QOL information will be collected quarterly for 12 months after the stroke event in the form of EQ-5D. Cost/utilization data will be collected at baseline, discharge, and the end of 3, 6, 9 and 12 months. The UB 04 form from the hospital will be collected at discharge for estimating the utilization during hospitalization. The quarterly healthcare resource utilization information will involve face-to-face surveys before discharge and at the end of 3 months, and phone surveys at 6th, 9th, and 12th month. The surveys will be administered to both the patient and a proxy. Literature strongly supports the collection of utilization data every 3-4 months for complex chronic conditions in order to collect unbiased patient recall information,[39-41] hence this study collects patient-reported utilization information every 3 months.

7.I.3.b. Survival and Healthcare Utilization Analyses. Survival will be analyzed using Cox proportional hazards models, adjusting for baseline covariates NIHSS, age, pre-morbid mRS, and previous TIA/stroke. We will also adjust for any additional baseline covariates that are imbalanced between treatment groups. If there are too many covariates to include in the model we will use a prescreening approach, testing covariates at the 0.20 level and including those that meet the latter criteria for significance. We will use both graphical methods[53] and statistical tests to check the proportional hazards assumption of the Cox regression model.

We will first use the graphic methods for detecting violations of the proportional hazards assumption. The plot of survival curves are based on the Cox Model and Kaplan-Meier estimates for each subgroup decided by covariates. Clear departures of two estimates indicate evidence against the assumption of proportional hazards. Another plot to be used is the plot of difference of the log cumulative baseline hazards versus time. Under proportional hazards, this plot is constant over time and centered on the estimated log-hazard ratio. Any time trend of the difference will suggest the violation of the proportionality assumption. Note that both plots only inform us if baseline hazards are proportional or not, and do not give detailed information about the type of departure from the proportionality. The plot of martingale residuals could be applied to determine the functional form to be used for a given covariate to best explain its effect on survival through a Cox proportional hazards model. The best functional form could be a transformation of the covariates (Z), such as log Z, or it may be a discretized version of the covariate. Under this situation, the martingale residuals are useful for determining cut points for the covariates. For example, we assume that Z1 is a single covariate of the covariate vector Z for which we are unsure of what functional form of Z1 to use. Let f(Z1) be the best function of the covariate Z1 to explain on survival. To find the form of the function f, we will fit the data based on Z and compute the martingale residuals. Then we plot these residuals against the values of Z1. The smoothed-fitted curve then gives an indication of the best function. For example, if the plot is linear, no transformation of Z1 is needed. If the plot is a piece-wise constant, then a discretized version of Z1 is suggested.

To formally test the assumption of the proportional hazards for the treatment effect, we will generate a time treatment interaction and refit the model to include the time treatment interaction. If the effect of the time treatment interaction is significantly different from zero, then the proportionality assumption is violated, and we will include a time treatment interaction in the model and choose the appropriate non-parametric approach[54].

Unadjusted and adjusted logistic regression analysis will be performed to estimate the difference in odds of 1) being re-hospitalized, 2) occurrence of any other overnight stay in a medical facility (including long-term acute care hospital, inpatient rehabilitation, skilled nursing facility,

intermediate care nursing home, or hospice care), and 3) occurrence of ED visits during the first year after discharge from the primary stroke hospitalization, between the MSU and the SM group. The adjusted logistic regression analysis will be adjusted for baseline demographic, socio-economic and clinical characteristics mentioned above.

8. Data Management

8.A. Data collection. Direct data collection begins at time of screening and continues until it has been determined that the subject is not eligible for this trial, the patient or family refuses consent, the patient drops out of the study, or completes the study. Until deemed ineligible, data from subjects are collected and reviewed for screening purposes. Data on eligibility are submitted to the DCC to allow a description of screened versus enrolled subjects. **Figure 1** shows the type and timing of data collected.

Data are collected on all subjects who have consented to continue in the trial. Data are collected using standardized case report forms. After data collection, the data are entered into to a secure, web-based data system designed for this trial. The web-based program provides the flexibility of entering data from multiple locations and centralizes the data management process. To ensure security, each user is assigned a username and password and this username, date and time of each login is recorded in a login history file to ensure a record is maintained of each access to the system. This information is also recorded in the change history audit logs. The data entered for the BEST-MSU trial are maintained in a secure database at the DCC.

Selected elements from the medical records (radiology reports, OR notes, patient history, morbidity and mortality notes, etc.) are collected in a HIPPA compliant manner. For subjects discharged to another facility, the clinical research staff completes an authorization form to release protected health information (PHI) and obtain signatures from the subject or LAR prior to discharge.

The subjects will be identified by a study number only. All hard copy source documentation will be kept in a secured, locked cabinet on site in the research coordinator‘s office. All study documents will be maintained in a secure location for two years following study completion unless superseded by participating site‘s requirement. The electronic data will be entered and maintained on a password protected web-based program designed for this trial.

The data entered for the trial will be maintained at the Data Coordinating Center (DCC) in a relational database cluster. The cluster is composed of multiple servers, which provide redundant access to the data in the event of a hardware failure to one of the servers. This cluster is maintained behind a firewall, which is not accessible from the internet without a secure network connection. The data will be backed up nightly and copies of the data will be routinely stored off site. In addition to the data servers, the production web server will also be backed up routinely. The separate development web server will serve as a backup to the production server.

8.B. Error checking. Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Checks will be developed by both clinical and DCC investigators. Depending on the question, any item found that does not meet the respective edit criteria will have an appropriate error message displayed when the user tries to save the data. Errors will be classified as either “hard” errors meaning that a valid response is required before the data can be saved or as “soft” errors in which the entry operator can either correct the errors or override them to indicate that the data are correct although it does not meet the edit criteria. Examples of hard errors would be items such as identifiers and event dates. An example of a soft error would be values that are outside a pre-defined range. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are currently four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors. For the first status, the entry user will have the option to save a record as “incomplete” for situations where they have partially entered a form and must stop because of an interruption. This will allow the user or the study coordinator to pull up the form at a later time and finish completing it. If the form was entered without any errors, then the record will be saved as complete. If the user overrides any soft errors found, the record will be saved as “saved with errors”. Staff in the DCC will have web-access to listings of subject specific errors needing correction by site. These errors can be corrected at the site or in the offices of the DCC (given documentation of the change). All site investigators will be trained to follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once a follow-up about any errors has been done by the DCC and the error has been corrected or certified as accurate, the status will be change to “complete with errors.” Once a record has been saved by the site or DCC as complete, they will no longer be allowed to make changes to the records. Any changes that result from obtaining new information woul by the staff at the DCC. At

the end of the trial after all possible corrections are made, the database will be locked and further changes will not be made.

8.C. Error correction follow-ups. Since there are times when data does not meet the required edit criteria such as out of range values, the site still needs to be able to save their data. However, such errors need to be followed up to ensure that the error was not by mistake. In this case, any soft error indicated will be logged to an error log data table through which the clinics can later generate a report of these errors that must be followed up on. This report will include the option for the clinic user to enter the correct value(s) if the record was saved by mistake or to indicate that the value saved was correct in which case they must provide an explanation as to why the error was overridden. These reports must be transmitted back to the DCC where staff will process the corrections through an error log management system. This process is particularly important for clarifying missing data. Once these reports are received back by the DCC staff and processed, the respective data record will be updated to the forth status of "complete with errors." Since clinical staff must verify these reports, these reports will serve as audit records should the funding agency need to investigate the process.

8.D. Data sharing plan. Once the database is locked for analyses and primary study publications are completed, the DCC will follow NINDS guidelines related to archiving de-identified data and making it publically available when requested by the NINDS. Furthermore, our protocol is designed is coordination with other centers in North American and Europe, with similar endpoints and study methodology to allow pooling of data.

8.E. Quality assurance. Training of research staff and nurses who will be responsible for recruitment and randomization of subjects is planned for the BEST-MSU study and in line with standard procedures. A standard manual of operations (MOO) developed by the DCC's research team will provide standard definitions of all study variables (i.e., data elements) and describe all data collection and data entry procedures in detail. The manual will be used in training the site's research team and will be available on the study website. In addition to the planned training meetings, the site will be responsible for the complete education of their personnel in the conduct of the BEST-MSU study.

8.F. Adverse events. According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject participating in a clinical trial. An AE can therefore be any unfavourable and unintended sign, symptom, injury or disease, whether or not related to the trial intervention (in this case, use of the MSU).

Adverse Events collected between study enrollment and hospital discharge

- tPA adverse reaction including angioedema
- Myocardial Infarction
- Respiratory Failure requiring intubation while on board the MSU
- Systemic Hemorrhage requiring transfusion or prolonged hospitalization
- Brain Bleeding
- New onset: Serious Arrhythmia with hemodynamic instability while on board the MSU
- Post IA Complication
- Fall or injury while on board the MSU
- Neuroworsening due to treatment while on board the MSU
- Other: Possibly related to involvement of MSU study

Adverse Events collected through 90 Days

- Death

8.F.1. Serious adverse event

A serious adverse event (SAE) is one that:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.

8.F.2. Adverse event observation and documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject's medical records. In this trial, all AEs that occur after the subject has signed the informed consent document will be documented on the pages provided in the CRF. In addition, all AEs that occur pre-hospital either in the MSU or during EMS transport will also be recorded. All subjects who have AEs, whether considered associated with the use of the MSU or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up by the time of resolve or normalization of changed laboratory parameters or until it has changed to a stable condition.
The intensity of an AE should be assessed by the investigator as follows:

mild:	temporary event which is tolerated well by the subject.
moderate:	event which results in discomfort for the subject and impairs his/her normal activity.
severe:	event which results in substantial impairment of normal activities of subject.

The investigator will evaluate each AE regarding the coherency with the trial treatment possibly exist:

definite:	if there is a reasonable possibility that the event may have been caused by trial participation. A certain event has a strong temporal relationship and an alternative cause is unlikely.
possible	An AE that has a reasonable possibility that the event may have been caused by the trial participation. The AE has a timely relationship to the trial treatments, however, follows no known pattern of response, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.
probable:	An AE that has a reasonable possibility that the event is likely to have been caused by trial participation. The AE has a timely relationship to the trial treatment(s) and follows a known pattern of response, but a potential alternative cause may be present.
unlikely:	Only a remote connection exists between the trial treatment and the reported adverse event. Other conditions including illness, progression or

expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.

unrelated: An AE that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.

not assessed: inadequate data for assessment, no other data may be expected

8.F.3. Reporting of Serious Adverse Events by Investigator

SAEs must be reported to the Data Coordinating Center, Clinical Coordinating Center and the Principle Investigator within 72 hours after the SAE becomes known.

9. Ceretom CT Scanner

The operation and safety of the Ceretom CT scanner will comply with all state and institutional licensure and regulatory standards. The Ceretom machine will be operated by a certified radiology technician. All training and safety measures will comply with Texas Administrative Code 289.227, Use of Radiation Machines in the Healing Arts, Texas Regulations for Control of Radiation. The Safety, Inspection and Health regulations regarding the Ceretom machine will be managed by UT Health Radiation Safety Program.

Safety Manager, Radiation Safety Program
Environmental Health & Safety
The University of Texas Health Science Center at Houston (UTHSC-H)
6431 Fannin St CYF G102
Houston, TX 77030
713-500-5844

10. Liability

The legal and liability compliance of the operation and patient care on the Mobile Stroke Unit, delegated staff members and patient care and/or treatment will comply with all state and institutional licensure and regulatory standards. All legal and liability compliance regulations regarding the MSU will be managed by UT Office of Legal Affairs.

Office of Legal Affairs
7000 Fannin, STE 1460
Houston, TX 77030
(713) 500-3281

and

Memorial Hermann Lifeflight
Chief Operating Officer
6411 Fannin
Houston, Texas 77030
713-704-0006

11. Project Milestones and Timeline.

As noted previously, our Mobile Stroke Unit was delivered in February 2014. We began the project with the expectation that additional external funding would be necessary to complete the study, and that we would need to amend the protocol based on our "run-in" experience and requirements of future funding sources. After the run-in phase, we decided to go ahead and begin the randomized study rather than interrupting our operations for several reasons: 1. To put the MSU into service and carry out the run-in phase, we had to establish a close collaboration with our major stake-holder—HFD-EMS. This included extensive training of EMS personnel and establishing a complex collaborative communication system. Furthermore, once we started deployment, EMS personnel quickly embraced the process and began to expect our responsiveness to their calls. For these reasons, we concluded that momentum would be lost and further cooperation of EMS would be jeopardized by interrupting the study to await further funding; 2. We had incorporated patients and community leaders in fundraising, conceptualization and setting up the study, and they strongly endorsed continuing MSU operations without interruption; 3. We had hired staff for the MSU who we would have to lay off if we interrupted service; 4. We concluded that if we offered full time MSU service for any prolonged period of time without beginning randomization, it would be difficult to subsequently justify randomization in the future; and 5. The MSU process and initial attempts at randomization were so successful that we realized only minor changes in the protocol were needed for the randomized phase, mainly pertaining to statistical analysis. Therefore, we began randomization of patients into the BEST-MSU study and data collection on August 18, 2014 (see Section C.6 Patient Recruitment). As will be described in more detail in the Budget Justification, our initial funding from local donors and industry is insufficient to carry us through

the end of calendar year 2016. This application is for funding to complete the study, including the addition of two more centers, to support additional community involvement, and ensure blinding and rigor in study conduct and data analysis.

Milestones

Study setup and progress to date-Houston:

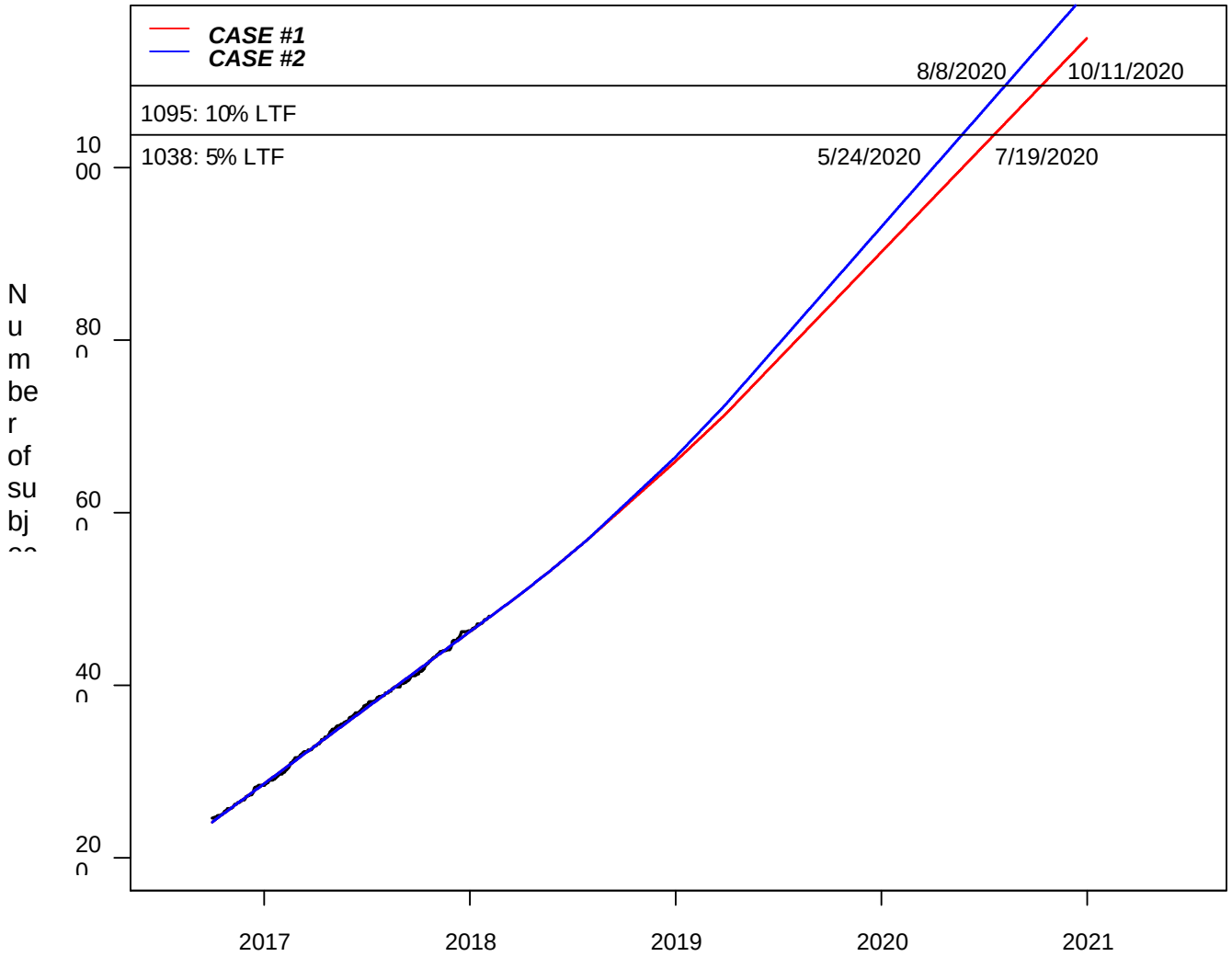
- *Protocol approval by UT Committee for Protection of Human Subjects 11/1/13*
- *Establishment of Case Report Forms 1/1/14*
- *Start of weekly Operations Committee meetings 1/1/14*
- *State and city licensing and radiation safety inspections completed 4/1/14*
- *MSU staffing and supplies completed 5/1/14*
- *EMS in-servicing complete 5/1/14*
- *Start of weekly Steering Committee phone meetings 5/1/14*
- *Start MSU patient treatment "run-in" phase in Houston 5/16/14*
- *Registration with ClinicalTrials.gov (NCT 02190500) 7/9/14*
- *Start of randomized phase of study in Houston 8/18/14*
- *First SMC meeting 2/4/15*
- *OpenClinica database established at DCC 3/1/15*
- *Second SMC meeting 8/31/15*
- *First Patient and Stakeholder meeting and formation of Patient Stakeholder Advisory Subcommittee 9/2/15*
- *Participate in yearly Texas state EMS conference (recurs yearly) 11/22/15*
- *Third SMC meeting 12/2/15*
- *Second PSAS meeting 1/18/16*
- *Approval of protocol amendment #1 by CPHS 1/21/16*

Colorado (Aurora and Colorado Springs), Memphis, Los Angeles, and San Francisco startup:

- *Colorado MSU delivered 7/30/15*
- *Colorado project manager hired 9/1/15*
- *Aurora licensing and inspections complete 12/1/15*
- *Aurora staffing and supplies complete 1/1/16*
- *"Go-live" in Aurora 1/13/16*
- *Aurora EMS in-servicing complete 2/1/16*
- *Colorado IRB approval 3/1/16*
- *"Go-live" in Colorado Springs 7/1/16*
- *Colorado enrollment begins 9/1/16*
- *Memphis project manager hired 1/1/16*
- *Memphis MSU delivered 3/1/16*
- *Memphis licensing and inspections complete 6/1/16*
- *Memphis staffing and supplies complete 6/1/16*
- *Memphis EMS in-servicing complete 6/1/16*
- *Memphis "Go-live" 7/1/16*
- *Memphis enrollment begins 9/1/16*
- *New York/Los Angeles MSU delivery 8/2017*
- *New Yorkl/Los Angeles IRB approval 12/2017*
- *New York/Los Angeles licensing and inspections complete 10/2017*
- *New York/Los Angeles "Go-live" Spring 2018*
- *Los Angeles enrollment begins April 30, 2018*
- *New York enrollment begins May 1, 2018*

- ***Sutter Health MSU delivery Feb/2018***
- ***Sutter Health IRB approval*** ***July 2018***
- ***Sutter Health licensing and inspections complete*** ***August 2018***
- ***Sutter Health "Go-live"*** ***August 2018***
- ***Sutter Health enrollment begins (October)*** ***TBD***
-

Current and Projected enrollment of tPA–eligible patients at all sites. Case 1 = enrollment of 1-1.5 patient per month at new sites. Case 2 = enrollment of 2 patients per month at new sites



12. **Patient Population**

Please see sections on patient identification, patient selection, patient recruitment, and representativeness of participants, subgroups, and engagement of stakeholders. In our overall randomized database to date, 25% of patients enrolled are > 80 yo (mean 68 yrs), 50% female; 44% African American, 16% Hispanic, median NIHSS 11 (IQ 6-20), 29% with baseline mRS ≥ 2.

Recruitment Plan

Total number of study participants expected to be screened:	10000
Total number of study participants expected to be enrolled of those screened:	2000
Target sample size (tPA eligible) of those screened and enrolled:	1038

Estimated Final Racial/Ethnic and Gender Enrollment

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native			
Asian	26	26	52
Black/African-American	208	207	415
Hawaiian/Pacific Islander			
White	285	286	571
Multirace			
Ethnicity	**Male (N)**	**Fema**	**Total (N)**

Hispanic (Latino/Latina)	83	83	166
Non-Hispanic	436	436	872

13. **Research Team and Environment.**

F.1. Mobile Stroke Unit (MSU) Consortium. The MSU Consortium is responsible for the oversight of the Houston MSU. To enlist the cooperation of all parties including the hospitals, academic programs, and EMS, Dr Grotta formed the MSU Consortium which is comprised of all principle stake-holders in the Houston MSU program; UTHealth (the owner of the MSU), Memorial Hermann Hospital-TMC (the licensor of the MSU under its Life Flight program), other CSCs in the TMC (that will receive patients and participate in the study), HFD-EMS (who will collaborate with the MSU team in patient management), Frazer Limited (which has built and donated the MSU), and patient representatives.

F.2. BEST-MSU Study Governance and staff (see Appendix 6 for organizational chart). The BEST-MSU study will have a single Houston **Clinical Coordinating Center (CCC)** and single Houston **Data Coordinating Center (DCC).** The study will be governed by a single Houston **Steering Committee (SC)** which will be comprised of Drs Grotta (P.I.) and Stephanie Parker RN (Project Manager) from the CCC, Jose-Miguel Yamal PhD (Co P.I.) and Suja S. Rajan PhD from the DCC, David Persse MD (HFD-EMS stakeholder representative), and James McIngvale (patient/community representative). The SC will oversee the execution of the study. The SC will meet by phone weekly, with written agenda and minutes, and have an in-person meeting quarterly. As the Denver and Memphis sites come on board the study, their P.I.s (William Jones MD and Andrei Alexandrov MD) will be added to the SC.

In addition there will be a **Patient/Stakeholder Advisory Subcommittee (PSAS)** comprised of 4 EMS and 4 patient representatives at each site. The PSASs will send quarterly reports to the SC, and meet with the SC in-person or via webex at their quarterly meeting (see Engagement section G). Updates on engagement activities at all sites will be shared at these quarterly meetings to encourage cross-semination of ideas.

The BEST-MSU Study day-to-day operations will be overseen by the **Houston CCC.** The Houston CCC will be comprised of Dr Grotta, Tzu-Ching Wu MD (telemedicine), Ritvij Bowry MD, Stephanie Parker RN, and Sherrie McCollum (Administrator). The Houston CCC meets weekly and is in charge of MSU staffing, scheduling, maintenance, operations, interaction with EMS, interaction with the DCC, and clinical coordination oversight of the Denver and Memphis sites.

Denver and Memphis will each have a **site Operations Committee** (**sOC**) comprised of their PI, Project Manager and other local personnel as indicated. The Houston CCC and sOCs will communicate by phone weekly (and prn) on study progress/problems at each site, and each sOC will provide a quarterly report on study conduct at their site to the SC. The Denver and Memphis sOCs will form their own local PSASs, and PSAS activities will be included in the report from each sOC to the SC.

The BEST-MSU Study **DCC** is comprised of Jose-Miguel Yamal PhD (Director), Suja S. Rajan PhD, and Barbara Tilley PhD. The DCC members will meet weekly and will be in charge of randomization, form development, database design and management, site training, monitoring and QA, and data analysis. The DCC will receive data directly from each site, and coordinate all database issues with the sites thru the Houston CCC. The DCC will provide quarterly reports on data management and study conduct to the SC and Study Monitoring Committee. All communications from the DCC to the SC, CCC or sOCs will contain only masked data.

The **Blinded Adjudicator** for the study will be Nicole Gonzales MD, Associate Professor of Neurology at UTHealth; a vascular neurologist otherwise unrelated to study management.

The BEST-MSU study will have a **Study Monitoring Committee (SMC)** comprised of David Lairson PhD Professor of Health Economics at the UTSPH (chair), Steven Levine MD, an international leader in Vascular Neurology and acute stroke treatment, telemedicine, and clinical trial conduct, and Robin Brey MD, Chair of Neurology at UT San Antonio and experienced clinical researcher and collaborator with Dr Grotta on telemedicine projects in Texas. In addition, a patient member of the PSAS will serve on the SMC. The SMC will meet quarterly (by web/teleconference) or more frequently if necessary, and receive the same quarterly reports from the DCC and OCs that are sent to the SC, and will report back to the SC any concerns or recommendations. The SMC will particularly focus on patient recruitment and retention, data integrity, protocol adherence, and safety issues, focusing on adverse events and reasons for lost to follow up. In addition, the SMC will be available to the SC for advice on any study related issues that arise.

The MSU is staffed by a Vascular Neurologist (VN--Dr. Grotta, Bowry or another VN from the participating CSCs experienced in clinical research, and familiar with study design and MSU operations), a Registered Nurse (RN--Ms Parker or another RN experienced in acute stroke care and clinical research), a Registered radiology CT technician, and a licensed HFD-EMS Paramedic working on the MSU while off regular duty hours. All physicians, nurses, paramedics and radiology technicians staffing the MSU hold appropriate Texas state practitioners licenses, have liability insurance, have passed their Advanced Cardiac Life Support training and Human Research and Good Clinical Practice Certifications, and are educated on the protection of human subjects.

James Grotta M.D. (Co-P.I.). Dr Grotta is overall P.I. Since 2013, the establishment and operation of the Houston MSU program and the BEST-MSU study has been Dr. Grotta's main priority, occupying 75% of his time.

Jose-Miguel Yamal, PhD (Co-PI). Dr Yamal is Associate Professor at the UT School of Public Health and has been the director of the DCC for this trial and has designed the analysis plan.

Suja S. Rajan, PhD (Co-I). Dr Rajan is Assistant Professor at the UT School of Public Health. She is a Health Services Researcher and Econometrician who will oversee the healthcare utilization, survival and quality of life analyses.

Stephanie Parker RN (Co-I. Project manager). Ms Parker is an experienced neuro-critical care nurse and clinical research coordinator, and has been project manager of the MSU program, primarily responsible for getting the project through regulatory and administrative hurdles while equipping and staffing the unit, working with EMS in developing dispatch and communication strategy, educating the paramedics, and designing the case report forms for the trial.

Tzu-Ching Wu MD (Co-I). Dr Wu is Assistant Professor of Neurology at UTHealth and director of its 16 hospital TM program. He will oversee all TM operations on the MSU and advise on TM operations at the other sites.

Ritvij Bowry MD (Co-I). Dr Bowry recently completed his VN fellowship and is currently completing his Neurocritical care fellowship at UTHealth. Starting 7/1/16, he will be an Assistant Professor of Neurology. Dr Bowry currently helps staff the MSU and will assist Dr Grotta and Dr Wu in providing VN and TM coverage on the MSU. He is first author of the publication describing the "run-in" phase of our study recently published in *Stroke*.

Nicole Gonzales MD (Co-I). Dr Gonzales is a VN and Associate Professor of Neurology at UTHealth. Dr Gonzales is an experienced clinician and clinical researcher, making her ideally suited to serve as the blinded adjudicator for patient inclusion into the study.

Andrew Barreto MD (Co-I). Dr Barreto is a VN and Associate Professor of Neurology at UTHealth. Dr Barreto is PI of the Argatroban rtPA Stroke Study (ARTSS). He is an expert in clinical trial design helping with the design of this study. He will also help Dr Grotta staff the MSU.

Barbara Tilley PhD (Co-I). Dr Tilley, a longstanding leader in clinical trial design and analysis and chair of the division of Biostatistics at UTSPH will be available to assist Dr Yamal in overseeing the DCC.

David Lairson PhD (SMC chair-consultant). Dr Lairson is head of Center for Health Services Research at the UTSPH and is chair of the SMC.

Steven Levine MD (SMC-consultant). Dr Levine directs the stroke service at SUNY Downstate, and is an experienced clinical trialist with a focus on acute stroke management. He serves on the SMC.

Robin Brey MD (SMC-consultant). Dr Brey is chair of Neurology at UT San Antonio. She is an experienced stroke clinical trialist and serves on the SMC.

William Jones MD (PI-Denver Site), Andrei Alexandrov (PI-Memphis Site) see biosketches.

David Persse MD (Medical Director EMS for the City of Houston—Stakeholder representative). Dr Persse is a long- time collaborator with Dr Grotta in pre-hospital organization of stroke care for the city of Houston. Dr Persse has facilitated the establishment of our system of communication with EMS dispatch, and has enabled our interactions with the EMT and paramedic corps under his command.

James McIngvale (Patient representative). Mr McIngvale, stroke survivor and local businessman/philanthropist, was instrumental in formulating the study with Dr Grotta and providing patient level feedback and financial support. He will serve on the SC as the main patient representative.

Laura Richardson (CEO Frazer Ltd-Stakeholder representative). Ms Richardson has provided expertise on MSU design, manufacture, buildout, and marketing. She will be the main business stakeholder.

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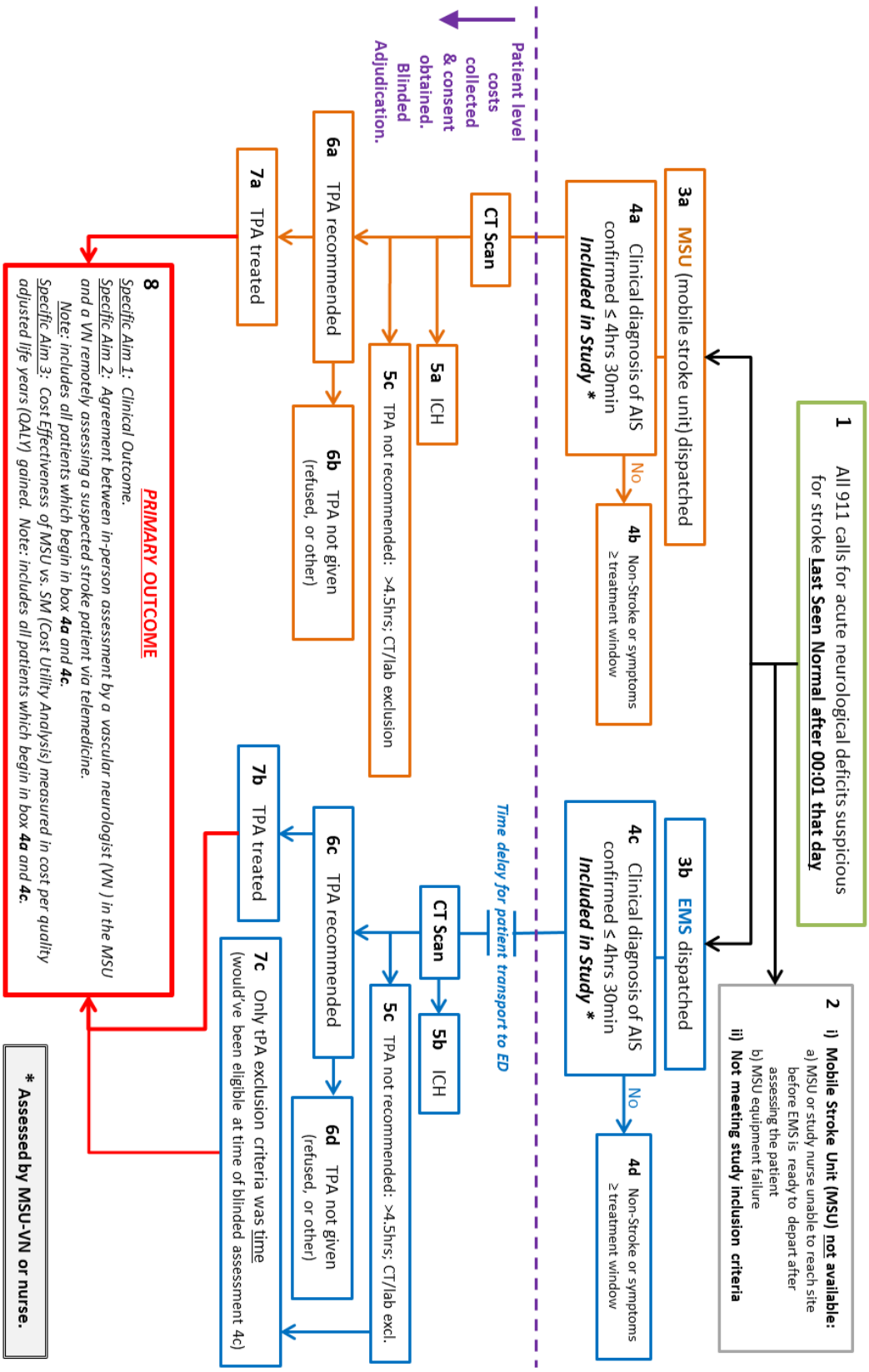
Appendix 1- Study Flow Chart



Appendix 2—Informed Consent

BEnefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study

(MOBILE STROKE UNIT)
HSC-MS-13-0322

INVITATION TO TAKE PART

You are invited to take part in a national research project called, **BE**nefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study, conducted by James Grotta, MD, and collaborators at the University of Texas Health Science Center at Houston, Baylor College of Medicine, Memorial Hermann Hospital System, St Lukes Hospital, The Methodist Hospital System, Harris Health System, Houston Fire Department Emergency Medical Services, West University Fire Department Emergency Medical Services, and Bellaire Fire Department Emergency Medical Services. For this research project, he will be called the Principal Investigator or PI.

Your decision to take part, or continuing to taking part, in this study is voluntary. You may refuse to take part or choose to stop from taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from any hospital, physician, health care entity, or Emergency Medical Service (EMS).

You may refuse to answer any questions asked or written on any forms. This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-13-0322.

PURPOSE

The purpose of this research study is to compare receiving standard emergency stroke treatment for ischemic or hemorrhagic stroke (a stroke caused by a blocked or bleeding artery in the brain) in a Mobile Stroke Unit (MSU), with standard emergency stroke treatment in a hospital, and to determine which has a better outcome and is more cost effective.

The standard, FDA approved emergency treatment for ischemic stroke is to give a drug called Activase®/Alteplase using an IV (in your vein). The standard in treating hemorrhagic stroke is to decrease systolic blood pressure to ≤ 150 with medications administered through the IV. With the help of a Mobile Stroke Unit, these treatments can be offered to patients having an ischemic or hemorrhagic stroke at the emergency site instead of at the hospital. This research study will try to determine if the mobile treatment option will save time and if it is safe. You are being invited to take part in the study because you may have experienced an ischemic or hemorrhagic stroke and a call was placed to 911 in order to provide assistance to you.

This is a multi-center national study. The study will enroll a total of 2000 subjects.

PROCEDURES

All treatment procedures completed during this study are standard of care. If you agree to take part in this study, or to continue to take part in this study, you will allow the research team to review some of your medical records from the treatment of your ischemic or hemorrhagic stroke, whether you were treated in the Mobile Service Unit (MSU) or at a stroke center hospital after being transported by the local Emergency Medical Service (EMS).

How the Mobile Stroke Unit Works
The MSU is dispatched along with EMS every other week in certain areas, during the hours of 8am to 6pm, Tuesday through Monday.

When the MSU is dispatched, standard treatment for ischemic and hemorrhagic stroke is given inside the mobile unit. This includes: a CT scan of the head, blood draws for lab tests, and treatment with, Activase®/Alteplase, Idarucizumab, or Prothrombin complex (depending on the type of stroke). Afterwards, the EMS ambulance will transport patients to the nearest stroke center hospital to continue care.

There are nine follow-up visits for this study. After 24 hours, a member of the study team will perform some cognitive tests, the National Institute of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (Rankin scale) to determine if you have had brain damage or have neurological deficits. The study team will also visit you on days 2 and 3, and the final day of your hospital stay to see if you have had or are still having complications. The study team will also call you by telephone to check on you at 30 days, ask that you come in to Dr. Grotta's clinic at 90 days after your stroke for a physical exam, and cognitive tests, in addition to a telephone call at 6, 9 and 12 months after your stroke.

TIME COMMITMENT

The total amount of time you will take part in this research study is up to one year after your stroke. Each study visit will last about 10-15 minutes.

BENEFITS

You may receive no direct benefit from taking part in this study. However, providing faster treatment within a Mobile Stroke Unit may reduce the negative outcomes associated with strokes.

RISKS AND/OR DISCOMFORTS

There are no additional risks to taking part in this research study other than those that are associated with the standard treatment for ischemic stroke. These risks will be explained to you by the physician that treats you or the PI. There is a possible risk of breach of confidentiality for taking part in this study.

ALTERNATIVES

The only alternative is to not take part in the study.

STUDY WITHDRAWAL

Your decision to take part is voluntary. You may decide to stop taking part in the study at any time. A decision not to take part or to stop being a part of the research study will not change the services available to you from Dr. James Grotta, emergency services, or area hospitals. The information obtained previous to withdrawal or study end will be used for data collection and analysis purposes; however the study team will not collect any more data after you withdraw from the study.

IN CASE OF INJURY

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Dr. James Grotta and to the Committee for the Protection of Human Subjects at (713) 500-7943. You will not give up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT AND COMPENSATION

You will not be paid for taking part in this study. All standard of care procedures will be billed to your insurance company. You will not incur any additional medical costs outside the standard of care treatment to participate in this study.

If you receive a bill that you believe is related to your taking part in this research study, please contact Stephanie Parker,MHA, BSN, RN at 713-500-6116 with any questions.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration (FDA), the Committee for the Protection of Human Subjects, Patient Centered Outcomes Research Institute (PCORI), Genentech, CSL Behring, Boehringer Ingelheim, may review your research and/or medical records for the purposes of verifying research data, and will potentially see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of the date of birth, subject initials, and treatment/service dates. You will not be personally identified in any reports or publications that may result from this study. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information. You will not be personally identified in any reports or publications that may result from this study.

NEW INFORMATION

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to stay in the study. This information will be provided to you during clinic visits or by phone.

Once the study is complete, the final results of the study will be sent to you via mail. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at anytime.

QUESTIONS

If you have questions at any time about this research study, please feel free to contact Dr. James Grotta 832-325-7296 or Stephanie Parker BSN, RN Program Director at 713-500-6116, as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research.

AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH

PATIENT NAME:_____ **DATE OF BIRTH:**_____

Protocol Number and Title: **BE**nefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study(HSC-MS-13-0322)

Principal Investigator: James Grotta, MD

If you sign this document, you give permission to The University of Texas Health Science Center at Houston, Memorial Hermann Healthcare System, HCA West Houston, Harris Health, Ben Taub, Houston Fire Department, Bellaire Fire Department, West University Fire Department, St. Luke's Hospital or Baylor College of Medicine to use or disclose (release) your health information that identifies you for the research study named above.

The health information that we may use or disclose (release) for this research includes *all information in a medical record with the exception of personal identifiers (name, address or personal identification)*

If you sign this document, you give permission to the researchers to obtain health information from the following healthcare providers:

☐ Memorial Hermann Hospital
6411 Fannin Street
Houston, Texas 77030

☐ St. Luke's Hospital and/or Baylor College of Medicine
6624 Fannin Street
Houston, Texas 77030

☐ The Methodist Hospital
6565 Fannin Street
Houston, Texas

☐ Ben Taub/Harris Health
1504 Taub Loop
Houston, Texas 77030

☐ Memorial Hermann-Memorial City
921 Gessner Road
Houston, Texas 77024

☐ Memorial Hermann-Southwest
7600 Beechnut Street
Houston, Texas 77074

☐ Memorial Hermann-Katy
23900 Katy Frwy
Katy, Texas 77494

☐ HCA West Houston
12141 Richmond Ave.
Houston, Texas 77082

☐ Houston Methodist West
18500 Katy Frwy
Houston, Texas 77094

☐ Houston Fire Department

☐ Bellaire Fire Department

☐ West University Fire Department

The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston for the purposes of verifying research records. The researchers may also disclose information to the following entities:

- Food and Drug Administration (FDA)
- Patient Centered Outcomes Research Institute (PCORI)
- National Institute of Neurological Disease
- Genentech
- CSL Behring
- IschemaView
- Boehringer Ingelheim

The University of Texas Health Science Center at Houston, Memorial Hermann Healthcare System, Ben Taub, Harris Health, Methodist, St. Luke's Hospital AND/OR Baylor College of Medicine are required by law to protect your health information. By signing this document, you authorize The University of Texas Health Science Center at Houston, Memorial Hermann Healthcare System, St. Luke's Hospital, Ben Taub, Harris Health, The Methodist Hospital System, AND/OR Baylor College of Medicine to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws

(such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. The University of Texas Health Science Center, Memorial Hermann Healthcare System, St. Luke's Hospital System, AND/OR Baylor College of Medicine may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to:
Dr. James Grotta
Director, Mobile Stroke Unit Consortium
UT Professional Building
6410 Fannin St, Suite 1423
Houston, Texas 77030
Fax: 713 500 7014

This Authorization will expire 15 years after the end of the study.

SIGNATURES

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

_____
Printed Name of Subject or Legally Authorized Representative

_____ _____ _____
Signature of Subject or Legally Authorized Representative Date Time

_____
Printed Name of Person Obtaining Informed Consent

_____ _____ _____
Signature of Person Obtaining Informed Consent Date Time

CPHS STATEMENT: This study (HSC-MS-13-0322) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

Appendix 3- IAT Protocol

Original Approved Date: December 18th, 2012 Revised Date: March 20, 2013, February 15, 2015

Endovascular Protocol

1. Age ≥ 18
2. Baseline mRS ≤ 3
3. NIHSS ≥ 8 (done within 60 minutes of groin puncture)
4. CT--CT, CTA, ?CTP (done within 60 minutes of groin puncture)
   ASPECT Score ≥ 6
   Large artery occlusion (distal ICA, M1, A1, proximal M2)
5. Use of Stentrievers; avoid general anesthesia
6. Time
   < 1 hour qualifying CT and NIHSS to groin puncture
   < 6 hours symptom onset to presumed groin puncture in anterior circulation
   < 12 hours symptom onset to presumed groin puncture in posterior circulation

Appendix 4—ICH substudy

A Prospective study of early hemorrhage enlargement (EHE) and its treatment on the Mobile Stroke Unit (MSU) vs standard Emergency Department (ED) treatment (HEME-MSU Study).

Introduction and Background:

Active bleeding leading to hematoma enlargement (HE) occurs early after Intracerebral Hemorrhage.

Early studies conducted before the wide availability of CT scanning suggested that the period of active bleeding in ICH is rather brief (<1 hour),[1] and the observation of clinical deterioration after admission was frequently attributed to the effects of brain edema, although instances of continuous bleeding were occasionally reported.[2] A number of subsequent CT studies of the early phases of ICH have helped to clarify these concepts.

Broderick et al[3] evaluated eight patients with ICH by CT within 2.5 hours of onset and again several hours later (within 12 hours of onset in seven patients), documenting a substantial increase in hematoma size (mean percentage increase, 107%). This increase in the volume of the hemorrhage was accompanied by clinical deterioration in six of the eight patients, all of whom had a 40% increase in hematoma volume. In five patients, the clinical deterioration occurred with blood pressure measurements of 195 mm Hg or higher. These investigators suggested that a prolongation of active bleeding for several hours (up to 5 or 6 hours) after onset may not be uncommon as a mechanism of early clinical deterioration in ICH. Similarly, Fehr and Anderson[4] reviewed 56 cases of hypertensive ICH in the basal ganglia and thalamus and documented enlargement of the hematoma with CT in four (7%); in two of the four, the increase in hematoma size was documented within 24 hours from onset, and in the other two, it was documented on days 5 and 6. Three of the patients had neurologic deterioration. In two who experienced deterioration within 24 hours, it occurred in the setting of poorly controlled hypertension, whereas the others had adequate blood pressure control. One of two patients with adequate blood pressure control was a chronic alcoholic, leading the investigators to suggest that alcoholism may be a risk factor for delayed progression of ICH.

Three subsequent studies further clarified the patterns of early enlargement of ICH. Fujii et al[5] studied 419 patients with ICH, in whom they performed the first CT within 24 hours of onset and the follow-up CT within 24 hours of admission, which showed hematoma enlargement in 60 patients (14.3%). Kazui et al[6] conducted sequential CT evaluations in 204 patients with acute ICH, documenting enlargement of at least 12.5 cm^3, or by 40% of the original volume, in 20% of the cases. The highest frequency of detection of hematoma enlargement was seen in patients in whom the initial CT scan was performed within 3 hours of stroke onset (36%); the detection of enlargement declined progressively as the time from ICH onset to first CT increased, and there was no documentation of enlargement in those first scanned more than 24 hours after onset. These observations suggest that the period of hematoma enlargement can extend for a number of hours from onset as a result of active bleeding, which is a phenomenon that is frequently, but not always, associated with clinical deterioration. The study reported by Brott et al[7] involved 103 patients in whom first CT scans were obtained within 3 hours of ICH onset and follow-up CT scans were obtained 1 hour and 20 hours after the initial scans. ICH enlargement (>33% volume increase) was detected in 26% of patients at the 1-hour follow-up scan, and an additional 12% showed enlargement between the 1-hour and 20-hour CT scans. The change in hematoma volume was often associated with clinical deterioration, but there were exceptions. These researchers found no predictors of ICH enlargement, evaluating age, hemorrhage location, severity of initial clinical deficit, systolic and diastolic blood pressure at onset or history of hypertension, use of antiplatelet drugs, platelet counts, prothrombin time, and partial thromboplastin time. In addition to more frequent hematoma enlargement early after onset, a recent study showed that hematoma growth was also quicker (i.e. the bleeding was more rapid) the earlier after onset patients were imaged.[8]

Finally, we have observed that HE is accompanied by a failure to mount the normal pro-coagulant response to bleeding as measured by thrombelastography (TEG).[9]

While these studies documented the importance of HE, and that it is more frequent and severe the earlier it is sought, no studies to date have evaluated HE in the first 1-2 hours after onset of ICH. Extrapolating from clinical data described above, it is very likely that HE will be even more frequent during the first hour after bleeding starts, and that interventions to limit bleeding might be most effective during this time interval. The advent of the Mobile Stroke Unit (MSU) where patients are evaluated and imaged within the first hour after onset of symptoms will make it possible for the first time to examine the natural history of this early hematoma enlargement (EHE), the use of TEG as a predictor of EHE, and the effect of interventions to limit it.

Aim 1: Use the MSU platform to evaluate the natural history of EHE

1a. We hypothesize that significantly more EHE will occur in the first two hours after symptom onset compared to later.

1a.i. The number of patients with EHE will be more.

1a.ii. The volume of EHE will be more.

All patients with ICH scanned on the MSU will have a repeat CT 1 hour after the initial CT. We will determine the number of patients with EHE, and the average volume of EHE, in patients scanned within the first 2 hours (and in the 0-1 hour and 1-2 hour groups separately), and compare results to those scanned 2-4 hours after onset.

1b. We hypothesize that there will be significantly smaller hematoma volume in patients having initial scan within 2 hours of symptom onset compared to those scanned 2-4 hours either on the MSU or in the ED.

Patients will be included if they have baseline CT carried out within 4 hours of symptom onset, whether initially scanned on the MSU or in the ED. The difference in average volume between those with baseline scan within 2 hours of symptom onset vs those scanned 2- 4 hours after onset will represent the average volume of EHE occurring during the time interval between the two populations (The 0-2 hour group will be analyzed as a whole, and also the 0-1 and 1-2 hour groups separately).

Rationale —HE is associated with worse outcome after either hypertensive or coagulopathic ICH. Most HE occurs within the first few hours after onset (see summary of literature above), but is probably grossly underestimated since patients are rarely seen and scanned within the first hour or so after onset when HE is most likely to occur. Early hematoma enlargement (EHE) occurring in the first 1-2 hours after bleeding onset may be much more frequent, proportionately larger in volume, and have a more important effect on outcome than HE during the ensuing hours. However, knowledge about EHE is limited as it is very rare to capture patients in this hyperacute period. MSU management will allow us for the first time to asses EHE.

Aim 2: Investigate the effect of early blood pressure (BP) control or coagulation reversal in ICH patients on EHE. Patients with at least one SBP reading >150, INR > 1.4, or use of Dabigatran within the prior 48 hours will be included in this Aim.

2a. We hypothesize that BP treatment (or coagulopathy reversal) within the first 2 hours after onset, as facilitated by the MSU, will reduce the number of patients having EHE.

2b. We hypothesize that BP treatment (or coagulopathy reversal) within the first 2 hours after onset, as facilitated by the MSU, will reduce the volume of EHE.

Patients will be included if they have baseline CT carried out within 4 hours of symptom onset, whether initially scanned on the MSU or in the ED. We will compare number of patients who

develop EHE and change in hematoma volume from baseline to 24 hours in patients having BP treatment (or coagulopathy reversal) begun within the first 2 hours after symptom onset (the 0-2 hour group will be analyzed as a whole, and also the 0-1 and 1-2 hour groups separately) to what is expected. Similarly, we will compare the same outcomes for those treated in the 2-4 hour group to the expected number of patients with EHE and expected change in hematoma volume. The expected incidence of EHE and amount of hematoma growth will be calculated based on what is observed from the untreated patients in SA1 and compared to their respective 0-2 hour or 2-4 hour group. The difference in number of patients with EHE, and in average volume, will represent the number of patients with EHE and the average volume of EHE prevented by earlier management. The proportion of patients in the 0-2 hour and 2-4 hour group treated in the MSU versus ED will be calculated.

Rationale --BP lowering is currently being tested to prevent HE after hypertensive ICH, and drugs are now available (4 Factor Prothrombin Complex Concentrate-4F-PCC and Praxbind) to rapidly reverse the coagulopathy caused by warfarin (4F-PCC) or by other newer oral anticoagulants like Dabigatran (Praxbind), or Factor Xa Inhibitors such as Apixaban or Rivaroxaban (4F-PCC, Andexanet). Current standard management is to lower the SBP in our ED to 130-150 mm Hg or to give 4F-PCC (for elevated INR or when the concurrent use of a Factor Xa I is suspected) or Praxbind (when the concurrent use of Dabigatran is suspected) once ICH is confirmed on CT scan. Guidelines also recommend Andexanet if available in place of 4F-PCC when the concurrent use of a Factor Xa I is suspected. In both the aggressive and standard treatment arms of ATACH, patients will probably receive lowering of SBP to about 150 mm Hg (and lower in the aggressive treatment arm) after arrival to the ED. However, therapy begun in the ED will not result in BP lowering (or coagulopathy reversal) within the first hour of onset, and rarely within the first 2 hours. MSU management will permit such early BP lowering (or coagulopathy reversal) and allow us to assess its results on preventing EHE.

Aim 3: Determine if coagulation status, as measured by thromboelastography (TEG), is more altered very early after the onset of spontaneous (non-coagulopathic) ICH compared to later, and if TEG predicts EHE.

3a. We hypothesize that the pro-coagulation response to ICH will be greater soon after the onset of bleeding.

3b. We hypothesize that patients without early pro-coagulation changes on TEG will be more likely to develop EHE.

We will compare TEG values in MSU patients studied within the first 2 hours after symptom onset to those studied later, and in patients with EHE to those without. Patients with bleeding due to known coagulopathy or antithrombotic therapy will be excluded from this Aim.

Rationale -- We have shown that ICH is associated with faster and stronger clot formation as measured by TEG, but that patients with HE do not demonstrate this presumably adaptive response to bleeding. It is possible that failure to mount this hypercoaguable state after ICH may be important in leading to HE. This dynamic has never been studied in the first hours after ICH onset when EHE may be more frequent and dramatic than later HE. MSU management will allow us to obtain TEG measurements in the first hours after ICH onset and correlate them with EHE.

Inclusion Criteria:

1. Enrollment into MSU study (meeting all inclusion criteria)
2. Parenchymal ICH on first CT scan < 60cc
3. At least one SBP reading >150 or INR > 1.4 (only for SA 2)

Exclusion Criteria:

1. Primary or predominant IVH, SAH, or SDH
2. IVH with filling of >50% of the lateral ventricle

Interventions:

Group 1: Patients transported on the MSU found to have ICH on CT will receive protocolized BP treatment with Nicardipine or Labetalol to reduce SBP to 140-150 mm Hg in the MSU before arrival to ED. Patients will also receive treatment with 4F-PCC if INR > 1.4, or Praxbind, if Dabigatran is used within the prior 48 hours. If Apixaban or Rivaroxaban is used within the prior 48 hours, patients will receinve 4F-PCC, or Andexanet if it is available.

Group 2: Patients in the SM arm of the MSU study (no MSU deployment) later found to have ICH after CT in the ED will receive pre-hospital treatment as per EMS routine (control of SBP to no lower than 180 mm Hg using labetalol) followed by standard management of BP, elevated INR, or other anticoagulant use in ED

Primary Outcomes <u>(All hematoma volumes measured by the AXBXC/2 method):</u>

Aim 1:

1. Incidence of hematoma expansion(defined as increase in hematoma size by > 6cc or by 30%) and volume of EHE (ICH volume on 1 hour follow up scan – ICH volume on initial CT) in Group 1 patients who had initial CT scan within 4 hours of onset. 'EHE' will be used to indicate hematoma expansion occurring in patients captured within 2 hours from onset and 'HE' will be used to indicate hematoma expansion that is captured later. We will analyze the entire group of patients scanned within 2 hours as a whole, and also those scanned within 1 hour and between 1-2 hours separately, and compare with those scanned later. We will evaluate coagulopathic and non-coagulopathic related ICH patients separately.

2. Difference in average hematoma volume on baseline scans between 0-2 hour and 2-4 hour patients (Group 1 or 2). We will analyze the entire group of patients scanned within 2 hours as a whole, and also those scanned within 1 hour and between 1-2 hours separately, and compare with those scanned later. The difference in average volume will represent the average volume of EHE occurring during the time interval between the two populations. We will evaluate coagulopathic, and non-coagulopathic related ICH patients separately.

Aim 2:

1. Incidence of EHE/HE and change in hematoma volume from baseline to 24 (+ 12 hr) hours in patients having BP treatment (or coagulopathy reversal) started within 2 hours and 2-4 hours of symptom onset (Group 1 or 2) compared to what is expected for each respective time group . We will analyze the entire group of patients treated within 2 hours as a whole, and also those treated within 1 hour and between 1-2 hours separately. We will also calculate the proportion of patients in each group with treatment begun on the MSU. The difference in number of patients with EHE, and in average volume, will represent the number of patients with EHE and the average volume of EHE prevented by earlier (mainly MSU) management.

Aim 3:

1. We will obtain TEG values (R, K, MA, Angle, Delta) in all Group 1 patients with spontaneous ICH (normal INR and no use of DTIs or Factor Xa inhibitors) comparing parameters in those with blood drawn within the first 2 hours versus 2-4 hours after symptom onset, and in patients with EHE to those without in the 0-2 hour group. We will analyze the entire group of patients analyzed within 2 hours of symptom onset as a whole, and also those analyzed within 1 hour and between 1-2 hours separately.

Other variables to be measured in both Group 1 and Group 2 patients:

1. Symptom onset time
2. Time of enrollment into either MSU or SM arm pre-hospital
3. Time of all CT scans
4. Hematoma volume, morphology and location on all scans
5. Etiology of ICH
6. Group 1: BP levels and treatment in MSU and ED for first 2 hours . Group 2: BP levels and treatment by EMS and ED up to the time of first CT scan
7. Time from symptom onset to first BP treatment and to first SBP < 150
8. Dose and time of any 4F-PCC or Praxbind administration
9. NIHSS at time of all CT scans (baseline in both groups, 1 hr CT in Group 1), and at 24 hrs in all pts.
10. Use of antiplatelet drugs
11. Significant comorbidities, chronic HTN, coagulopathy
12. Modified Rankin score at 90 days
13. TEG, other baseline coagulation measurements (platelets, INR, PTT)

Sample Size Estimation and Methods (All analyses adjusted for baseline NIHSS, use of antiplatelets, comorbidities; Use logarithmic transformation of hematoma volume to normalize the distribution):

Aim 1a. If we assume a 30% incidence of HE in the 2-4 hour group, and expect an increase to 60% in the 0-2 hour group, a total of 94 patients (47 per group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Aim 1b. Based on previous studies, the mean $\pm$ SD of the logarithmic hematoma volume in the 2-4 hour group should be 2.9 $\pm$ 1.2. If we expect 30% smaller baseline hematoma volumes in the 0-2 hour group log vol = 2.0), to achieve 80% power, a total of 64 patients (32 per group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Aim 2a. The expected incidence of EHE/HE and volume of hematoma growth will be derived from patients who present within 4 hours of onset (separated into 0-2 hour and 2-4 hour groups) who do not receive acute BP treatment or coagulopathy reversal. If we assume a 60% incidence of EHE in the 0-2 hour group and expect early BP treatment (or coagulopathy reversal) to reduce this to 30%, a total of 94 patients (47 per group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Aim 3. We have previously studied TEG values in ICH patients presenting within 6 hours of onset and compared TEG values for those who developed HE to those who did not. K, which represents speed of clot formation, was significantly slower in patients with HE, with a mean difference of 1.5 $\pm$ 3.1 min. Assuming mean K in the 2-4 hour group will be 1.5 min longer than the 0-2 group and that there will be a 1.5 min difference between HE and non -HE patients, then we would expect a 3 min difference between the 0-2 hour EHE patients and the 2-4 hour non-HE patients. A total of 40 patients (20 in each group) adjusting for multivariable analyses will be needed to achieve 80% power to detect this difference with a 0.05 two sided significance value.

Procedures:

1. Get baseline MSU CT loaded onto PACS for measurement.
2. Obtain careful documentation of BP and BP treatment X first 2 hours Group 1 and up to time of first CT scan in Group 2.
3. Obtain accurate history of previous meds, comorbidities, coags, baseline NIHSS and mRS.
4. Obtain TEG in all Group 1 pts.
5. Obtain 1 hr f/u CT and NIHSS in all Group 1 patients.
6. Obtain 24hr CT and NIHSS in all pts.
7. Modified Rankin Score (mRS) at 90 days.

References:

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Appendix 5—Interosseous tPA administration substudy

Intraosseous administration of tPA for the BEST-MSU Study (IO-MSU Substudy)

I. Background and Rationale

The current protocol for HSC-MS-13-0322, the Be*nefits of Stroke Treatment Delivered Using a Mobile Stroke Unit Compared to Standard Management by Emergency Medical Services: The BEST-MSU Study,* requires intravenous (IV) administration of alteplase. In an urban prehospital setting, intravenous access by paramedics has an estimated initial attempt rate ranging from 77.4-89% success rate,[1,2] with an average time to insertion of 4.4 ± 2.8 minutes.[3] Intraosseous (IO) administration of medication offers an alternative to IV access in the prehosptial environment. Success rates for initial IO administration ranges from 84%-97% [4] [5] with the battery powered devices (EZ-IO) offering increased efficacy in speed of administration.[6]
Thrombolytics have been administered through the IO route safely for pulmonary embolism and myocardial infarction with no complications. [7] [8] The major concern for adverse effects relates to the potential for thrombolytic extravasation. Another case with both epinephrine and thrombolytic therapy through the IO resulted in significant soft tissue necrosis. [9] However the extravasation rates of drug administration from IO is a relatively rare occurrence if the needle is properly placed.[10] The goal of the emergency mobile stroke unit is efficacious and timely of administration of thrombolytic therapy.[11] This protocol addition to the current study will allow for IO placement and infusion of alteplase in patients who are unable to have an IV successfully placed after two attempts prehospitally.

Analysis
This protocol will utilize the patient level data collected from the BEST-MSU study. Only patients who had an IO placed with successful medication will be included. Analysis will include a report of the number of IV attempts made, the number of IO attempts made, and the record of success of infusion and in hospital complications related to the infusion.

II. Objectives
The primary objective of protocol is to provide IO as a route of alternative administration of alteplase in a patient without IV access.
Aims/Outcomes:
The investigators will assess the following outcomes from this protocol

- Number of IO lines place
- The number of successful infusions of alteplase via IO
- The number of complications related to IO infusion of alteplase.

In addition, this study will help to:

- Guide revisions or continued implementation of IO thrombolytic therapy both prehospital and in hospital.

III. Study Population
Inclusion criteria
All patients enrolled under the current HSC-MS-13-0322 trial who cannot have an IV placed successfully after two attempts.

Exclusion criteria:

- Infection of wound at site of IO placement
- Fracture or suspected fracture at IO site
- Previously attempted IO at site

IV. Protocol Design

All prior protocols from HSC-MS-13-0322 will remain unchanged. IV access will be attempted twice on a patient qualifying for alteplase administration based on the already established trial protocol. If IV access is unsuccessful, IO access will be attempted using the EZ-IO device at the proximal tibia , just medial and inferior to the anterior tibial tuberosity or the proximal humerous. The paramedic will be permitted a maximum of two attempts with IO. On second attempt the other tibial site must be used for placement. Prior to alteplase infusion, withdrawal and successful saline flush must be demonstrated to ensure proper IO placement. To reduce the pain that may be associated with initial infusion 10cc of 1% Lidocaine without epinephrine will be infused after verification of the IO line. The IO will be left in place until at least two hours after completion of the alteplase infusion. In the event of alteplase extravasation, the infusion will be stopped immediately, the IO will be left in place and saline will be infused through the IO.

V. Procedures

Data collection

The treating provider will report the number of IV and IO attempts if IV was failed to be placed

Data Analysis

Investigators will conduct data analysis to measure the outcomes and any adverse events associated with IO infusion

Reports and Publication

Investigators will participate in developing reports and research articles for academic and emergency medicine journals. Data will only be reported and/or published on an aggregated level.

VI. Benefits/Risks/Informed Consent

Benefits

Data generated from this outcomes research will potentially improve the care of stroke patients in the prehospital environment who require thrombolytic administration but are unable to have an IV established

Risks

The major risk is the potential for extravasation of alteplase through an incorrectly placed IO.

VII. References

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2. Spaite DW, Valenzuela TD, Criss EA, Meislin HW, Hinsberg P. A prospective in-field comparison of intravenous line placement by urban and nonurban emergency medical services personnel. *Ann Emerg Med*. 1994;24(2):209–214.

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11. Ebinger M, Kunz A, Wendt M, et al. Effects of Golden Hour Thrombolysis. *JAMA Neurol*. 2014. doi:10.1001/jamaneurol.2014.3188.

Appendix 6 – Genentech Safety Reporting

ASSESSMENT OF SAFETY

6.1 SPECIFICATION OF SAFETY VARIABLES

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to **Activase**, all events of death, and any study specific issue of concern.

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or other protocol-imposed intervention, regardless of attribution.
This includes the following:
 AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with treatment of acute ischemic stroke that were not present prior to the AE reporting period.

 If applicable, AEs that occur prior to assignment of study treatment associated with medication, no treatment run-in, or other ischemic stroke treatment. Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

6.1.2 Serious Adverse Events

An AE should be classified as an SAE if:
It results in death (i.e., the AE actually causes or leads to death).
It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
It requires or prolongs inpatient hospitalization.
It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

6.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in Section 5.1.1, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

6.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 90 days following the administration of treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior treatment.

6.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately.
Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the **Activase** (see following guidance), and actions taken.
To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:
Yes

There is a plausible temporal relationship between the onset of the AE and administration of the **Activase**, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the **Activase**; and/or the AE abates or resolves upon discontinuation of the **Activase** or dose reduction and, if applicable, reappears upon re-challenge.
No
Evidence exists that the AE has an etiology other than the **Activase** (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to **Activase** administration (e.g., cancer diagnosed 2 days after first dose of study drug).
Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.
Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

6.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

6.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:
"How have you felt since your last clinical visit?
"Have you had any new or changed health problems since you were last here?"

6.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). 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 ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. 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".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting 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 preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. 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 coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior **Activase** exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

h. SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below.
The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available. Serious AE reports that are related to the Activase will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date. Serious AE reports that are unrelated to the Activase will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date. Additional Reporting Requirements to Genentech include the following:
Any reports of pregnancy following the start of administration with the Activase will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date. All Non-serious Adverse Events originating from the Study will be forwarded on a quarterly report to Genentech.
Note: Investigators should also report events to their IRB as required.

j. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

QUERIES

Queries related to the Study will be answered by *Dr James Grotta.* However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. *Dr James Grotta* agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. *Dr James Grotta* agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.
Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.
In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.
Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

MedWatch 3500A Reporting Guidelines
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:
o Protocol description (and number, if assigned)
o Description of event, severity, treatment, and outcome if known
o Supportive laboratory results and diagnostics
o Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information
Additional information may be added to a previously submitted report by any of the following methods:
o Adding to the original MedWatch 3500A report and submitting it as follow-up
o Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
o Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.
MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
IRB NUMBER: HSC-MS-13-0322 IRB APPROVAL DATE: 02/18/2015
WHAT IS A PRODUCT COMPLAINT?
A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.
OTE TO FILE (v.4) 2
All complaints must be filed within 1 business day for pre-approved products and 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).
WHAT ELSE DO I NEED TO DO?
In order for Roche/Genentech to satisfy its regulatory obligations to the FDA, additional reporting requirements to Genentech are needed for all Investigator Initiated Studies (interventional and non-interventional).
If drug is being supplied for your study AND patients are still on treatment, but there is no Quality Agreement in place OR The Quality Agreement does not include the actions and responsibilities of Product Complaints, then an amendment to the protocol or SDEA (Safety Data Exchange Agreement) is required.
Please ensure your protocol or SDEA is updated at the time of the next amendment or by July 31, 2020, whichever is earlier. For any questions, please reach out to your MSL or Clinical Operations team.

Appendix 7 – Prospective pilot feasibility study of treating ICH on the MSU with Praxbind

Background

Blood pressure reduction and reversal of coagulopathies are part of the management of ICH, with drugs such as Praxbind, that can now rapidly reverse the coagulopathy caused by Dabigatran. Current standard management is to lower the systolic blood pressure (SBP) to 140 mm Hg and/or to give Praxbind once an ICH is confirmed on a CT scan and there is a history of concurrent Dabigatran use. MSU management will permit such early BP lowering and/or coagulopathy reversal as a result of Dabigatran and allow us to assess its results on preventing early HE. The current proposal to evaluate just the coagulopathy reversal portion of this project.

Hypothesis

In patients with ICH and use of Dabigatran, coagulopathy reversal within the first hours after onset, as facilitated by the MSU, is feasible and will prevent EHE compared to later treatment.

Protocol

Patients transported on the MSU with ICH < 60 cc on CT within 4.5 hours of symptom onset and use of Dabigatran will receive Praxbind per the treating physicians clinical judgment.

Praxbind dosing: Praxbind will administered as an intravenous dose of 5g (administered as 2 separate 2.5g doses no more than 15 minutes apart).

Inclusion criteria

a. Last seen normal possibly within 4hr 30 min of symptom onset
b. History and physical/neurological examination consistent with acute stroke
c. Parenchymal ICH on first CT scan < 60 cc (in MSU)
d. Use of Dabigatran

e. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment (BP or coagulopathy treatment) will not be delayed for consent; however, consent must eventually be obtained for data to be retained for analysis.

Exclusion criteria
a. Primary or predominant IVH, SAH, or SDH
b. Concurrent use of rivaroxaban, apixaban, coumadin or edoxaban

Variables to be measured in patients
1. Symptom onset time
2. Time of enrollment into MSU arm pre-hospital
3. Time of all CT scans
4. Hematoma volume, morphology and location on all scans. Volume to be measured both by AXBXC/2 and volumetric analysis.
5. Etiology of ICH
6. BP levels and treatment in MSU and ED for first 2 hours
7. Dose and time of Praxbind administration
8. NIHSS at time of all CT scans (baseline, 1 hr, and 24 hrs in all pts)
9. Use of antiplatelet drugs
10. Significant comorbidities, chronic HTN, coagulopathy, past medical history
11. Baseline coagulation measurements (Platelets, INR, PTT, thrombin time) if available
12. Modified Rankin score at 90 days (including mortality)

Primary objective
Feasibility of administering Praxbind in the mobile stroke unit.

Secondary objective
EHE in MSU treated patients. ICH volume (AXBXC/2 method) of first CT scan in MSU vs ICH volume of a second CT scan 2 hours later. EHE = > 30% increase from scan 1 to scan 2. Absolute change in hematoma volume for each patient between the two scans, and the mean change in volume between the two scans for the entire group. Other clinical endpoints will be collected including hospital length of stay, ICU length of stay, mortality, thromboembolic events, Rankin scores.

Sample size
3 patients treated with Praxbind (based on estimates of how many patients can potentially be treated from real world experience)

References
1. Herbstein DJ, Schaumburg HH: Hypertensive intracerebral hematoma: An investigation of the initial hemorrhage and rebleeding using chromium Cr 51-labeled erythrocytes, *Arch Neurol* 30:412, 1974.

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Appendix 8 – Prospective pilot feasibility study of administering Praxbind on the MSU for acute ischemic stroke

Background

Intravenous tissue plasminogen activator (IV tPA) is the standard treatment for acute ischemic stroke, with faster treatment times increasing the chances of better outcomes. Treatment on a mobile stroke unit (MSU) can expedite the delivery of IV tPA to patients who have symptoms within 4.5 hours and meet certain exclusion criteria that can increase the risk of hemorrhage. The concurrent use of Dabigatran is one such exclusion, although its effect can now be reversed by Praxbind. The administration of Praxbind to ischemic stroke patients taking Dabigatran on a MSU can allow for faster administration of tPA and thus increase the likelihood for improved outcomes in these patients.

Hypothesis

In patients with acute ischemic stroke taking Dabigatran, reversal with Praxbind on the MSU is feasible and can facilitate treatment with IV tPA.

Protocol

Patients transported on the MSU who have acute ischemic strokes within 4.5 hours of symptom onset and are taking Dabigatran will receive Praxbind per the treating physician's clinical judgment, followed by IV tPA (using standard dosing and inclusion/exclusion criteria for IV tPA).

Praxbind dosing: Praxbind will administered as an intravenous dose of 5g (administered as 2 separate 2.5g doses no more than 15 minutes apart).

Inclusion criteria

a. Last seen normal possibly within 4hr 30 min of symptom onset
b. History and physical/neurological examination consistent with acute stroke
c. No tPA exclusions per guidelines (except for Dabigatran use), prior to CT scan or baseline labs
d. Concurrent use of Dabigatran
e. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment (including IV tPA) will not be delayed for consent; however, consent must eventually be obtained for data to be retained for analysis.

Exclusion criteria

a. Any intracranial hemorrhage
b. Concurrent use of rivaroxaban, apixaban, coumadin or edoxaban

Variables to be measured in patients

1. Symptom onset time
2. Time of enrollment into MSU arm pre-hospital
3. Time of baseline CT scan
4. Time of Praxbind administration
5. Time of IV tPA administration

6. BP prior to and after Praxbind and tPA administration
7. NIHSS at time of all CT scans
8. Concurrent medications
9. Time and strength of last Dabigatran dose
10. Significant co-morbidities (chronic HTN, coagulopathy, other past medical history)
11. Baseline coagulation measurements (Platelets, INR, PTT, thrombin time) if available
12. Modified Rankin score at 90 days (including mortality)

Primary objective
Feasibility of administering Praxbind in the MSU.

Secondary objective
Safety of administering Praxbind in the MSU.

Sample size
3 patients treated with Praxbind (based on estimates of how many patients can potentially be treated from real world experience).

Appendix 9 – Boehringer-Ingelheim safety reporting

Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,

or

- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event..

Intensity of adverse event

The intensity of the AE should be judged based on the following:

• Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

• Moderate: Enough discomfort to cause interference with usual activity

• Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (

e)CRF , if they are judged clinically relevant by the investigator.

Responsibilities for SAE reporting to Boehringer-Ingelheim (BI)

The investigator shall report all SAEs, AESIs, non-serious AEs which are relevant to a reported SAE or AESI by using BI IIS SAE form and pregnancies using BI pregnancy monitoring form to BI Unique Entry Point by fax or other secure method in accordance with the timelines specified below as per the Pharmacovigilance agreement.

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;

- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

- Pregnancy Monitoring Forms shall be forwarded within seven (7) days

BI Unique Entry Point:
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridge bury Road
Ridgefield, CT 06877
Fax: 1-203-837-4329

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) Investigator Brochure for the Product.

The inclusion criteria for the study require the subject experiencing acute stroke with the concomitant use of Dabigatran. The investigators are responsible in reporting these adverse events to authorities and/or to Boehringer-Ingelheim as required, in compliance with local regulatory requirements for post marketing spontaneous reporting.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if investigator considers it as relevant to the BI study drug.

Appendix 10 - Substudy of Retrospective Acquisition of 90-day mRS

Rationale

When the 90-day mRS is not able to be obtained within the data collection window (90 days -7 days or +30 days) but the patient/family is contacted at a later date, a retrospective mRS could help to reduce missing data for the primary outcome. However, it is unclear whether collecting this retrospectively suffers from recall-bias or if it's a reasonable approach to imputing those outcomes.

Primary Aim

The goal of this substudy is to estimate the validity of acquiring the 90-day mRS at a later point of time when the patient has been lost at 90 days.

Secondary Aim

The secondary goal is to estimate the validity of acquiring the
1. 90 day EQ5D
2. quality of life
3. visual analog score at a later point of time when the patient has been lost at 90 days.

Approach

The 90-day mRS collected around 90 days after enrollment and either (a) retrospectively at 6 months, (b) retrospectively at 9 months, or (c) retrospectively at 12 months after hospital discharge. Two measurements per subject will be obtained and compared to each to see if the recall matches the actual mRS. To look for any decay, we will obtain the second mRS at either the 6 month, 9 month, or the 12 month visit, chosen randomly.
The same questions will be asked of the secondary outcomes.
To activate time-window specific memories, we would ask them to recollect how they were on particular specially memorable days that fell within the 2.5-3.5 month visit window, e.g. holidays (Valentine's Day, July 4, Thanksgiving, Christmas, etc) or family events (birthdays, anniversaries, etc).

Analysis

The mRS at 90 days will be compared to the retrospectively-obtained mRS using kappa statistics (if mRS is dichotomized or treated as categorical) or weighted Kappa statistics (if keep all categories and want to give some credit when the categories were close). This will be done separately for the comparisons of
- 3mo vs. 6mo
- 3mo vs. 9mo
- 3mo vs. 12mo mRS values.

STATISTICAL ANALYSIS PLAN (SAP)

BEnefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study

Houston Data Coordinating Center

PI: Jose-Miguel Yamal, PhD

Co-Investigator: Suja S. Rajan, PhD

UTHealth, School of Public Health

Houston, TX 77030

June 2017

updated March 2018 (sensitivity analysis of utility weights, adjusted analysis for TM subgroup analysis)

updated January 2019 (include a pre-specified subgroup of EMS arrival <1 hr vs >1hr from last seen normal)

updated February 2020 (include clarification of the modified ITT analysis and sensitivity analyses)

updated April 2020 (included 30% improvement from baseline to 24 hr NIHSS as a secondary outcome)

updated June 2020 (clarified the primary analysis as a regression model, including site adjustment and alternative modeling if assumptions are not met; added new utility weights)

Table of Contents

1. STUDY OVERVIEW

1.1. Objective and Study Design

The primary goal of this project is to carry out a trial comparing pre-hospital diagnosis and treatment of patients with stroke symptoms using a Mobile Stroke Unit (MSU) with subsequent transfer to a Comprehensive Stroke Center (CSC) Emergency Department (ED) for further management, to standard pre-hospital triage and transport by Emergency Medical Services (EMS) to a CSC ED for evaluation and treatment (Standard Management-SM).

There are many ways that use of a MSU might prove valuable in stroke patients, but we will focus on acute ischemic stroke (AIS) and treatment with IV tissue plasminogen activator (tPA) within 4.5 hours of symptom onset since that is the most evidence based effective emergency treatment for the most prevalent stroke diagnosis. We hypothesize that the MSU pathway will produce an overall shift towards earlier evaluation and treatment, particularly into the first hour after symptom onset, leading to substantially better outcome. We will also explore the hypothesis that as a result of improved clinical outcomes resulting from earlier treatment, the costs of a MSU program will be offset by a reduction in the costs of long term stroke care and increase in quality adjusted life years, thereby supporting more widespread use of this technology. To make MSU deployment more practical, we will confirm that a Vascular Neurologist (VN) on board the MSU can be replaced by a remote VN connected to the MSU by telemedicine (TM) thereby reducing manpower requirements and costs.

The successful completion of this project will provide data on important outcomes and costs associated with the use of MSU vs SM in the United States (U.S.) that will determine the value of integrating MSUs into the pre-hospital environment that would be more generalizable throughout the country. Therefore, the proposed study is the necessary step in a process that may dramatically modify the way that acute stroke patients are managed.

This is a prospective multicenter cohort study with randomized deployment weeks and blinded assessment of both trial entry and clinical outcomes.

2. DEFINITION OF TARGET POPULATION AND STUDY SAMPLES

2.1. Target Population

No. of Clinical Sites: 6
No. of subjects:

To be assessed for eligibility	(n = 4900)
To be enrolled	(n = 1845)
To be analyzed (“tPA eligible”)	(n = 1038)

Main criteria for inclusion:

1. Criteria for MSU team to **enroll** a patient into the study (to be determined pre-hospital on both MSU and SM weeks)

a. Last seen normal possibly within 4hr 30 min
b. History and physical/neurological examination consistent with acute stroke
c. No definite tPA exclusions per guidelines, prior to CT scan or baseline labs
d. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment, including IV tPA, will not be delayed for consent; however, consent in both MSU and SM patients must eventually be obtained for data to be retained for analysis.

2. Criteria for **tPA-eligibililty** (to be determined pre-hospital on MSU weeks, and after ED assessment on SM weeks, and confirmed by blinded adjudication)

a. Meeting tPA inclusion and exclusion criteria per guidelines after CT scan, baseline labs, and clinical re-evaluation

2.2. Study Outcomes

2.2.1. Primary Outcomes

- The utility-weighted modified Rankin Scale (mRS) at 90 days, comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks.

2.2.2. Secondary Outcomes

- Comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks.
    - ordinal (shift) analysis of mRS at 90 days, and
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS

- The agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation. N.B. Patients will include all enrolled patients on MSU weeks considered for tPA treatment.

- An exploratory cost-effectiveness analysis (CEA) of MSU versus SM using the Incremental Cost Effectiveness Ratio and Incremental Net Benefit estimate will be performed. N.B. The exploratory CEA will include all enrolled patients on MSU and SM weeks found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not)

- Comparing all patients treated with tPA (whether or not adjudicated as tPA eligible) on MSU weeks compared to patients on SM weeks.
    - Utility-weighted modified Rankin Scale (mRS) at 90 days
    - ordinal (shift) analysis of mRS at 90 days, and
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS

- Comparing enrolled patients treated with tPA within 60 minutes of LSN onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS) between the groups at the time of treatment. N.B. Patients will include only those patients actually treated with tPA based on the final determination of the time LSN, and will include only patients meeting all inclusion and exclusion criteria.
    - utility-weighted mRS at 90 days,
    - ordinal (shift) analysis of mRS at 90 days
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS
    - Instead of dichotomizing into two groups based on time from LSN to tPA, logistic regression of 90-day mRS 0,1 vs 2-6, using a restricted cubic spline for time from onset to treatment, with visualization of spline term compared with the odds ratio

- Comparing all patients treated with IAT (separate analyses for those adjudicated as tPA eligible, all tPA treated, or all IAT with or without tPA) on MSU weeks compared to patients on SM weeks.
    - utility-weighted mRS at 90 days
    - ordinal (shift) analysis of mRS at 90 days
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS

- The time from LSN to tPA treatment on all patients treated within 4.5 hours of LSN on MSU weeks compared to similarly eligible patients on SM weeks. N.B. Patients will include all enrolled patients actually treated with tPA (or on SM weeks, eligible for tPA treatment) meeting all inclusion and exclusion criteria, and based on the final determination of time of LSN. One analysis will compare the median times. A second analysis will also capture the patients who were eligible but did not receive tPA because it was too late, categorizing time into the following groups (e.g., 0-60min, 61-90min, 91min-180min, 181-270min, eligible but no tmt because>270).

- Of the enrolled patients that were eligible for treatment with tPA (according to

published guidelines) on MSU weeks compared to SM weeks, the percent that were treated within 4.5 hours and within 60 minutes of LSN.

- The time from LSN, from alarm time, and from ED arrival to start of endovascular procedure (intra-arterial thrombectomy-IAT) in patients who meet pre-specified criteria for IAT on MSU weeks compared to SM weeks. N.B. All patients receiving IAT will be included in this outcome.

- The proportion of all tPA-eligible patient having IAT on MSU weeks compared to SM weeks

- The median/mean time from LSN to tPA therapy decision on all patients considered for treatment within 4.5 hours of LSN on MSU weeks compared to SM weeks. N.B. Patients will include all enrolled patients meeting inclusion criteria whether or not treated with tPA.

- Time between 911 call and onset of etiology-specific BP management on MSU weeks compared to SM weeks. N.B. Patients will include all enrolled patients.

2.2.3. Safety Outcomes

- The incidence of symptomatic intracranial hemorrhage (sICH) in enrolled tPA treated patients on MSU weeks compared to SM weeks (Symptomatic intracranial hemorrhage defined as any intracranial blood accumulation associated with a clinical deterioration of $\geq$4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration) N.B. Patients will include all patients treated with tPA, whether or not they meet all inclusion and exclusion criteria.

- Mortality. N.B. All enrolled patients signing informed consent will be included in this endpoint and followed until 1 year.

- The incidence of stroke mimics and transient ischemic attacks (TIAs) in tPA-treated patients, and also in tPA-eligible patients, on MSU weeks compared to SM weeks. N.B. SM patients deemed eligible for tPA on their pre-hospital assessment who then completely recover by the time of arrival in the ED will equal the excess incidence of TIAs treated on the MSU pathway.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Randomization and Analytic Cohorts (The process is described in detail in the protocol)

Weeks when the MSU is available or not are randomly selected. Stroke events are orthogonal to whether the MSU was being deployed or not that week and thus participants will be randomly

entered into either the MSU or SM groups depending on when their stroke occurs.

The primary analytic cohort is based on a modified intention-to-treat (ITT) analysis where the subject will be assigned to the group that they were enrolled in (e.g. if a patient was enrolled using SM, they would be assigned to the SM group) and adjudicated (by the blinded adjudicator) to be tPA eligible. The usual ITT includes every subject who is randomized according to randomized treatment assignment. In this study, all patients within each group who are adjudicated as tPA eligible by an adjudicator blinded to group assignment are included. The randomized assignment is not conducted for each patient, rather we generally alternated weeks to be either MSU or SM weeks, which is independent of when a subject randomly has a stroke and calls 911. Therefore, this may be considered a cluster-randomized trial where the cluster is the days when the MSU is available and the other cluster is when MSU is not available. There is not anything clinically important to set the cluster of when the MSU was available or not as a week (e.g., an alternative design could set one week as having MWF as MSU days and TTH as SM days and the next week as the opposite), but this made it convenient to set work schedules and to have a similar amount of time dedicated to recruitment of MSU and SM subjects and there is not a scientific nor statistical rationale suggesting that the clusters would be related to the patient's outcomes and intervention effect. Patients are, in a sense, "randomly" allocated into the clusters based entirely on when they happen to have their stroke in relation to the prospectively determined cluster allotment of whether the MSU is available or not. Furthermore, in order to optimize the utilization of the MSU, some cities have 2 sites enrolling patients at the same time, with one site running the MSU and other enrolling SM patients and then they switch the next week.

There are a few cases when the MSU was not available during an "MSU week" (e.g. the unit is out of service on another call, had to be serviced for an oil change, staff were sick and therefore unable to come in) and stroke patients that were treated using standard management were enrolled into the study by the study team into the SM arm. These few subjects will be included in the primary analysis in the SM arm, but moved to the MSU arm in a sensitivity analysis (see section 5.1.3). The decision to include them in the primary analysis is based on a November, 2019 comparison of the SM subjects who were enrolled during an "MSU week" compared to the SM subjects enrolled during an "SM week". Baseline characteristics (age, sex, ethnicity, race, pre-stroke mRS, baseline NIHSS, tPA treatment, time from LSN to tPA bolus, endovascular treatment, and DTGP) were similar between the groups, confirming our belief that there should not be any added bias for including them in the primary analysis. The benefit of including them is to improve the MSU:SM ratio and to increase the chance of recruiting subjects according to the projected timeline. However, this analysis will be repeated at the end of the study to confirm that no significant differences exist between these two SM populations before including them in the MSU arm.

3.2. Blinding

Blinded assessment of both trial entry, tPA-eligibility, and study outcomes. All patients are screened for trial enrollment during their pre-hospital evaluation and management by the same investigators on both MSU and SM weeks to ensure that comparisons are made between similar patients, using similar criteria, at a similar stage of illness. For enrolled patients, criteria for study enrollment and tPA treatment are subsequently reviewed by a vascular neurologist (VN) blinded to MSU vs SM

assignment and not otherwise involved in study management or analysis. The blinded VN determines from a dedicated "adjudication form", omitting any time data or other information that would produce unblinding, if the patient meets criteria for study enrollment and for tPA treatment. For comparing outcomes between MSU and SM, we will only include tPA-eligible patients on both MSU and SM weeks, whether or not actually treated, based on this blinded review. Investigators obtaining all outcomes are blinded to treatment allocation.

3.3. Multiplicity

No adjustments for multiple comparisons will be made. However, the secondary analyses will be interpreted with caution.

4. SAMPLE SIZE DETERMINATION

4.1. Sample Size for the Phase III trial

The power of this trial was based on the difference in primary outcome, 90 d uw-mRS. Based on preliminary data, we expected 1.8 times as many MSU as SM patients because when we began the study, on SM weeks some patients were occasionally taken by EMS to non-participating stroke centers where they could not be enrolled into the study. On MSU weeks, these patients would be transported in the MSU only to participating hospitals and therefore enrolled. Subsequently, we have incorporated these non-participating hospitals into the study, thereby mitigating this gap and the groups are now balanced. With a sample size of 693 total tPA-eligible patients (446 MSU and 247 SM patients, assuming 10% lost to follow-up [LTF]), the study will have 80% power with a 0.05 Type I error to detect a difference between groups of 0.09 in the mean uw-mRS using a two-sample t-test. This difference is plausible and important. In a re-analysis of 11 acute stroke studies8, the difference in mean 90d uw-mRS between groups ranged from 0.024-0.25, with most positive trials in the range of 0.1. In the NINDS tPA trial, 90d uw-mRS difference was 0.09 between tPA and placebo.

In March, 2018, Dr. Grotta, blinded to study data, requested, and PCORI approved, an increased sample size to 1095 patients from the 693 initially requested, and to allow three additional sites to be added. This request was based on our reassessment of anticipated difference in 90 day uw-mRS based on a.) results of the Berlin non-randomized study which showed a 0.07 difference between MSU and control patients, b.) results of the DAWN trial which was the first completed study to use the uw-mRS, and c.) reanalysis of a substantial number of completed stroke trials where conventional mRS outcomes were translated to uw-mRS (see figure below). In that analysis, Broderick et al found that the smallest clinically meaningful difference was 0.04[1]. We based our initial sample size of 693 tPA eligible patients on the ability to detect a 0.09 point difference which was the same as between tPA and placebo in NINDS. The endovascular studies found a >0.10 point difference. Based on these pieces of information which were not available when we designed our study, Dr. Grotta reassessed the anticipated difference between groups if the MSU produces a substantial reduction in time to treatment, and felt that a difference of 0.07 is a more realistic goal. Dr. Yamal did not participate in that decision since he is unblinded.

Assuming a 3:2 (1.5) imbalance, 5% LTFU, and using the pooled standard deviation of STEMO & No STEMO group (sd=0.385), numbers of patients needed to detect a difference of 0.07using a 2-sample t-test is N=1038. Our LTFU so far has been around 5% so we expect this assumption to be reasonable. PCORI has agreed to the increase in sample size and sites sufficient to detect a 0.07 difference.

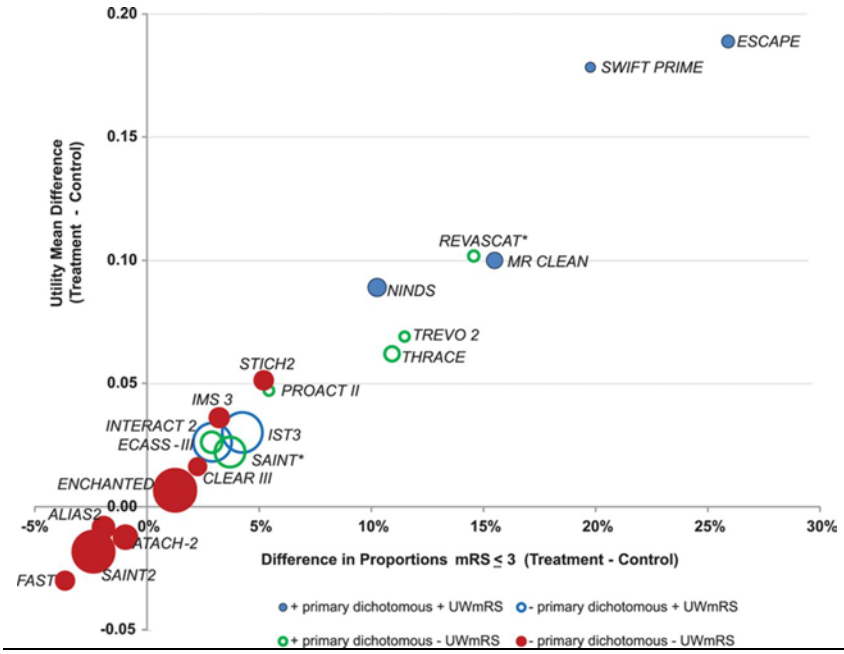

Figure. Reanalysis of a substantial number of completed stroke trials where conventional mRS outcomes were translated to uw-mRS. Effect sizes reported. From Broderick, et al.

4.2. **Sample Size Estimation for Cost Effectiveness Analysis**

We will perform an exploratory cost analysis using the cost data collected during this study. Based on the sample size estimation outlined in Willan et al[2], and cost and QALY estimations from past studies[3-6], we estimated a range of sample sizes that will be required for a formal CEA. The lowest and highest observed change in QALY in the literature was 5-20%; similarly observed change in cost was 10-25%. Based on these the sample size requirement in the most optimistic case was 96 patients (48 in each group) and in the most conservative case was 740 patients (370 in each group) for a power of 80% and p-value if 0.05. Approximately 50% of the patients for whom the MSU is dispatched, and who meet inclusion criteria for enrollment into the study, will receive tPA. Hence, the total number of patients used for the CEA will have to be between 192 and 1480 patients. Even though the current study probably will not meet the sample size requirement for the conservative case, it will help establish the expected cost and QALY changes for the MSU intervention (which have never been estimated before).

5. ANALYSIS PLAN

5.1. Phase III Trial Analysis

5.1.1. Treatment Group Comparability at Baseline

Although the random enrollment of participants to the two treatment arms and blinded review of tPA eligibility should ensure comparability with respect to known and unknown variables, imbalance may occur by chance. Descriptive statistics for baseline characteristics known or suspected to be associated with outcomes will be prepared for the two treatment groups for all randomized as well as all deemed "eligible for tPA" based on the blinded review. Chi-square statistics and Wilcoxon rank sum tests will be used to evaluate baseline differences between the arms for categorical and continuous variables, respectively. Any variables with baseline differences will be included in secondary adjusted analyses. Also, completers will be compared to non-completers (loss to follow-up for 90 mRS) on these baseline variables to indicate whether missingness may be considered random.

5.1.2. Primary Clinical Analysis

The mean uw-mRS at 90d along with corresponding two-sided 95% confidence intervals will be compared between groups using a two-sample t-test or Wilcoxon rank sum test if the assumption of normality does not hold. Although the mRS is an ordinal outcome, the difference between the uw-mRS categories has clinical significance and the t-test assumption and central limit theorem are likely satisfied. The primary analysis of uw-mRS will be adjusted for baseline uw-mRS, site, any baseline covariates that are different between the two groups, and covariates associated with mRS, including baseline NIHSS, age, pre-morbid mRS, and previous TIA/stroke, in a linear regression model. If the assumptions of the model are not satisfied, a restricted cubic spline will be used to model baseline continuous variables (NIHSS and age). If the linear regression with splines does not fit well, we will use ordinal logistic regression to adjust for the variables. If the proportional odds assumption fails, we will use logistic regression with mRS 0-1 vs 2-6 as the primary analysis. Assuming that the primary analysis doesn't use the following models, sensitivity analyses of the primary outcome will be conducted including ordinal (shift) analysis using a proportional odds model and proportion achieving a dichotomized outcome of mRS 0-1 vs 2-6 using binary logistic regression.

Utility weights

The sample size was originally designed using the Dawn trial utility weights that were derived based on a United Kingdom sample and using the 3-level version of EQ5D. EQ5D-5L has been in use for more than a decade. However, the corresponding population-level utility weights for 5L had not been developed for many countries, and most countries only have population-level weights for the much older EQ5D-3L. In 2019 a study was published by Pickard et al. conducted a survey to develop utilities based on a US population and using

the 5-level version of EQ5D (EQ5D-5L), which is more relevant to the participants in the BEST-MSU study. Using their Probit model estimated parameters to calculate utilities, in June 2020 we fit a linear regression model with these utilities (using 90-day EQ5D-5L) as the outcome and the 90-day mRS indicator variables as the independent variables to estimate our specific utility-weighted mRS. We also applied both the Dawn and the newly derived utility weights to the B-PROUD data and observed that results were consistent in the comparison of their mobile stroke unit data and their non-mobile stroke unit groups between these two weight choices. These were presented during the June 2020 study monitoring committee and were approved to use as the primary outcome of our trial. The weights based on the June 2020 data are presented in Table.

Table. Comparison of utility weights.

mRS	Dawn weights (previous MSU weights)	ENCHANTED trial weights	New proposed MSU
0	1	0.977	1
1	0.91	0.885	0.91
2	0.76	0.748	0.72
3	0.65	0.576	0.65
4	0.33	0.194	0.18
5	0	-0.174	0.05
6	0	0	0

5.1.3. Sensitivity Analysis of Primary Outcome

We will conduct sensitivity analyses using Dawn utility weights of the 90 day mRS. An additional sensitivity analysis will add an indicator of whether the SM subjects that were enrolled during an MSU week affect the treatment effect in a regression model by adding an indicator for these subjects. Also, in a sensitivity analysis, we will move these subjects into the MSU arm to check for consistency of results.

A further sensitivity analysis will remove subjects that were enrolled during the COVID-19 pandemic months (beginning of March, 2020).

5.1.4. Analyses of Ancillary Clinical Outcomes

We will also compare mRS at 90d (uw-mRS, Δ uw-mRS from baseline, ordinal (shift) analysis, and proportion achieving 0,1) in tPA treated patients treated within 60 minutes of LSN to patients treated 61-270 minutes, regardless of whether they were on MSU weeks vs. SM weeks. Patients on MSU weeks vs SM weeks will also be compared for differences in (a) the time from LSN to tPA treatment, (b) time from LSN, alarm time, and ED arrival to start of IAT, and for safety outcomes (i) mortality, (ii) symptomatic intracerebral

hemorrhage, and (iii) incidence of tPA treated stroke mimics and transient ischemic attacks.

A logistic regression model will be used to compare 90 day mRS 0,1 vs 2-6 of patients treated with tPA within 60 minutes of symptom onset to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS, age, premorbid mRS, and previous stroke/TIA incidence) between the groups at the time of treatment[8]. If baseline characteristics are significantly different between the two non-randomized groups, we will use propensity score analysis to limit potential bias. Also, we expect a higher incidence of spontaneous recovery (TIA) and stroke mimics may occur with earlier observation in the 0-60 minute group compared to those seen 61-270 minutes. The "natural history" of the incidence of spontaneous recovery and stroke mimics will be estimated from patients enrolled into the SM group, and will be considered in analyzing the comparison between patients treated with tPA within 0-60 min vs 61-270 min. Time to treatment and to endovascular procedures will be analyzed using Cox proportional hazards models, similarly to survival. Categorical outcomes will be analyzed using Fisher's exact test.

Unless there is sufficient power (predetermined before the analysis is begun) the approach to ancillary analysis will generally be the calculation of confidence limits on intervention group differences rather than formal tests of significance as the trial may not have high power to detect difference in all of these outcomes. However, these comparisons will add to the knowledge of the benefits and risks of the intervention.

5.1.5. Subgroup Analysis

Tests of effects within subgroups will be driven by clinical rationale. To reduce the potential for spurious results, we would test for a sub-group treatment interaction at a 0.2 critical level. Any subgroup analyses that are not pre-specified would be considered post hoc and reported as requiring confirmation in future studies. Estimates of the MSU effect will be obtained separately for pre-specified subgroups with significant treatment-by-subgroup interactions, using the methods described above. Pre-specified subgroups include (1) patients treated via TM versus on-site VN, (2) patients treated at various sites, (3) patients that had the EMS arrive (for SM) or MSU arrive (for MSU) within $\leq$1 hr and those that arrived >1hr of LSN, and (4) race. For (3), time will also be considered as a continuous variable and the interaction between time and MSU/SM will be assessed with transformations or restricted cubic splines of time used if appropriate).

When doing the TM subgroup analysis, we anticipate that there may be demographic differences between sites that are doing TM versus onboard VN. For this analysis we will conduct regression models, adjusting for baseline NIHSS, age, pre-morbid mRS, time since last seen normal, and previous TIA/stroke, in a linear regression model.

Analyses of post-randomization sub-groups are subject to many biases. Thus any analyses of post-randomization sub-groups, such as those treated with IAT, would be considered on

a case by case basis requiring tailored use of advanced statistical methods[9] and careful interpretation.

5.1.6. Missing Data

We expect no missing data for baseline measures. For 90-day assessments, extensive efforts will be made to ascertain the modified Rankin scores and mortality status, though we anticipate a 5% rate of lost to follow-up. We will perform several approaches for handling missing data. Characteristics of patients who are lost to follow-up will be compared to those that remain in the study to assess the degree of any selection bias, and sensitivity analyses will be performed to evaluate robustness of conclusions to the different missing data approaches. We will use multiple imputation for the final values assuming missing at random, depending on if any significant baseline differences exist between those observations that have a missing value or not. As sensitivity analyses we will report the data with and without imputation. Data will also be stratified according to their missing pattern (e.g., early termination, late termination, and follow-up completers) and variables representing these groups will be used as model covariates in adjusted analyses.

5.2. Cost Effectiveness Assessment

5.2.1. Approach and Methods used in Cost Analysis.

In order to establish an economic basis for a higher reimbursement from the healthcare payers for dispatching an MSU the following aspects have to be established:

- Does the MSU improve the post-discharge stroke severity and consequently improve average patient QALYs? Higher cost for an intervention can be better justified if associated with improved patient outcomes.
- Does the MSU reduce post-stroke healthcare utilization and consequently costs for the healthcare payers? Reduction of post-stroke healthcare utilization will subsequently save costs for the healthcare payers who pay for these utilizations. By identifying whether the healthcare payers save costs for stroke management due to the use of MSU (and determining the amount of post-stroke cost savings) the study can provide scientific evidence for supporting additional Medicare reimbursements for an MSU dispatch.
- What is the magnitude of the incremental fixed costs associated with MSU and the per-patient incremental fixed cost due the ambulance outfitting, CT, other equipment, and telemedicine technology, staffing requirements and paramedic training? Establishing the magnitude of incremental fixed cost per patient will help determine the justifiable amount of increased reimbursements to agencies operating the MSU and providers supporting its telemedicine capabilities.

5.2.2. Sample used for Cost Analysis

The cost-effectiveness analysis (CEA) will include all enrolled patients on MSU and SM weeks who meet criteria for tPA treatment whether or not they are eventually treated with tPA. We estimate that approximately 50% of enrolled patients will receive tPA in the MSU

and SM group. The non-tPA treated patients will probably not benefit much from MSU management and since the primary goal of the MSU is to ensure quicker administration of tPA, only those patients who meet criteria to receive tPA will be included in the cost analysis (for one year cost and QALY follow-up). The cost of operating the MSU for the remaining 50% of the patients who are not eligible for tPA administration will be included as fixed costs of operating the MSU, but these patients will not be followed-up once they are deemed ineligible to receive tPA inside the MSU or at the ED.

5.2.3. Perspective of the cost-effectiveness analysis (CEA)

The CEA will be performed from the perspective of the healthcare payers. If dispatching an MSU improves patient outcomes it should theoretically reduce post-stroke healthcare utilization and hence the reimbursement costs for the healthcare payers under the current payment policies, which do not include additional reimbursement for an MSU dispatch. If the study demonstrates improved effectiveness along with cost-savings or demonstrates improved effectiveness with limited increase in costs for the healthcare payers it will help justify the additional reimbursements for dispatching an MSU. This justification is vital for the financial viability of this high cost intervention and hence critical for the study.

5.2.4. Measure of Effectiveness

Stroke results in severe morbidity, disability and mortality in the American population.23 More than 70% of the stroke patients are unable to return to their pre-stroke life style, activities of daily living and employment. Thus, stroke has a permanent impact on the patient's QOL, thereby necessitating the use of a patient-centered effectiveness measure that considers both the quality and quantity of a patient's life, and is not limited to physician reported clinical measures or survival. Hence, QALYs will be used as the effectiveness measure. QALYs will be obtained through utility-weight conversions using the EuroQol's EQ-5D measure. ED-5D is preferred due to its standardized ease of conversion to QALYs.33,38 We considered the use of other QOL measures like Neuro-QoL. After communication with the Neuro-QoL research team it was established that Neuro-QoL has not been validated for conversion to QALYs. In addition, Neuro-QoL involves the reporting of 18 adult domains in the form of separate T-scores which should not be combined to form a single QOL measure further limiting the feasibility of QALY conversion. Since costs analysis requires QALYs and not QOL measures, Neuro-QoL and similar stroke-specific QOL measures, which cannot be converted to QALYs, are not used in this study.

5.2.5. Measure of Cost

The cost components include: 1) The incremental fixed costs associated with the MSU 2) The index hospitalization costs 3) The post-discharge cost during the first year after the stroke episode 4) Life-time costs after the first-year. The incremental fixed cost (component 1) for the MSU group will include cost of additional outfitting required to convert an ambulance into an MSU, cost of additional staffing changes for the agency

operating the MSU, provider/hospital-level infrastructure changes to accommodate the MSU, clinical staff training, EMS and dispatch training, and all trips performed by the MSU (whether they involve tPA eligible patients or not). The variable cost (cost per patient) will include components 2 to 4, and will be measured for all patients in the MSU and SM group who meet criteria for tPA treatment whether or not they are eventually treated with tPA. Microcosting (resources * local market value) will be applied to the estimation of incremental fixed cost (component 1) whereas gross costing (utilization * Medicare payments) will be used for the variable costs of post-stroke healthcare utilization in the first year (components 2 and 3). Life-time costs after the first year (component 4) will be simulated using Markov modeling based on evidence from the literature[10,11]. The fixed cost of CT scanners and telemedicine equipment will be amortized over the 10 year expected life of the equipment. Medicare reimbursement amounts for patients from different geographic areas will be adjusted to make them nationally representative by using the CMS geographic adjustment factor (for part A claims) and CMS geographic practice cost index (for part B claims).

5.2.6. Funding and Cost Analyses

The cost analyses will not be supported by the PCORI funding.

6. MONITORING FOR EFFECTIVENESS AND SAFETY

6.1. Overview

Interim analyses for safety (symptomatic hemorrhage), efficacy/futility (dichotomized mRS 0-1 vs. 2-6), and process (time from alarm until treatment decision) will be conducted when the 90-day mRS has been collected on 50% of the total number of patients that are adjudicated to be tPA-eligible.

6.2. Interim Analyses for Effectiveness

The efficacy interim analysis of the 90 day dichotomized mRS will be a 2-sample, 2-sided test of proportions using a Haybittle-Peto boundary (p=0.001). This will be conducted on the subset that are tPA-eligible based on the blinded adjudication.

6.3. Interim Analyses for Futility

The futility analysis of the 90 day dichotomized mRS (0-1 vs 2-6) will be a 2-sample, 1-sided, test of proportions. The futility analysis will compare patients in MSU weeks vs SM weeks (alpha=0.15). If we reject the null hypothesis that the percentage of favorable outcomes (mRS<2) in patients in the MSU weeks is greater than or equal to the percentage of favorable outcomes in patients in the SM weeks plus 10%, we conclude that completing the trial would likely be futile. The futility hypotheses are: $H_0: p_{MSU} - p_{SM} \geq \Delta$ versus $H_A: p_{MSU} - p_{SM} < \Delta$ where p_{MSU} and p_{SM} are the proportions of participants expected to have a favorable mRS

outcome in the MSU and SM groups, respectively, and Δ denotes the 10% increase in favorable outcomes over SM considered clinically meaningful. This will be conducted on the subset that are tPA-eligible based on the blinded adjudication.

6.4. Safety Analyses

Rates of symptomatic hemorrhage will be compared using a Fisher's exact test (alpha=0.05). This will be conducted on all enrolled tPA-treated patients, excluding any that had an ICH on their baseline CT scan.

6.5. Process Analysis

Time from alarm to treatment decision will be compared using a one-sided Wilcoxon rank sum test (alpha=0.05) to test if the time is longer for the MSU arm. This will be conducted on the subset that are tPA-eligible based on the blinded adjudication. MSU-by-site interaction terms will be included in a regression model to test if these differ by site and if the interactions are significant then within-site tests will be conducted.

7. REPORTING PROCEDURES

7.1. CONSORT Diagram

We will account for every subject randomized into the study using a CONSORT diagram.

7.2. Primary Reporting for the BEST-MSU Study

We will account for every subject randomized into the study using a CONSORT diagram. Primary reporting for the BEST-MSU study will follow the classic CONSORT Checklist items (see appendix).

7.3. SMC Reports

Standard format for SMC reports will be developed and sent to the SMC for review before the initial safety analyses are presented, and the format will be added as an appendix to this report.

7.4. Publications

Before the BEST-MSU CCC begins an analysis for a manuscript or presentation, the first author or writing group will have their hypotheses and analysis plan reviewed and approved by a designated team at the BEST-MSU DCC.

8. REFERENCES

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Appendix A: CONSORT Checklist

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

http://jama.ama-assn.org/site/misc/auinst_chk.pdf

STATISTICAL ANALYSIS PLAN (SAP)

BEnefits of **S**troke **T**reatment Delivered Using a **M**obile **S**troke **U**nit Compared to Standard Management by Emergency Medical Services: The **BEST-MSU** Study

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Co-Investigator: Suja S. Rajan, PhD
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June 2017

updated March 2018 (sensitivity analysis of utility weights, adjusted analysis for TM subgroup analysis)

updated January 2019 (include a pre-specified subgroup of EMS arrival <1 hr vs >1hr from last seen normal)

updated February 2020 (include clarification of the modified ITT analysis and sensitivity analyses)

updated April 2020 (included 30% improvement from baseline to 24 hr NIHSS as a secondary outcome)

updated June 2020 (clarified the primary analysis as a regression model, including site adjustment and alternative modeling if assumptions are not met; added new utility weights)

updated April 2021 (included propensity score analysis as a posthoc analysis for all outcomes; included analysis of all enrolled cohort and adjudicated enrolled excluding stroke mimics and hemorrhages)

Table of Contents

1. STUDY OVERVIEW

1.1. Objective and Study Design

The primary goal of this project is to carry out a trial comparing pre-hospital diagnosis and treatment of patients with stroke symptoms using a Mobile Stroke Unit (MSU) with subsequent transfer to a Comprehensive Stroke Center (CSC) Emergency Department (ED) for further management, to standard pre-hospital triage and transport by Emergency Medical Services (EMS) to a CSC ED for evaluation and treatment (Standard Management-SM).

There are many ways that use of a MSU might prove valuable in stroke patients, but we will focus on acute ischemic stroke (AIS) and treatment with IV tissue plasminogen activator (tPA) within 4.5 hours of symptom onset since that is the most evidence based effective emergency treatment for the most prevalent stroke diagnosis. We hypothesize that the MSU pathway will produce an overall shift towards earlier evaluation and treatment, particularly into the first hour after symptom onset, leading to substantially better outcome. We will also explore the hypothesis that as a result of improved clinical outcomes resulting from earlier treatment, the costs of a MSU program will be offset by a reduction in the costs of long term stroke care and increase in quality adjusted life years, thereby supporting more widespread use of this technology. To make MSU deployment more practical, we will confirm that a Vascular Neurologist (VN) on board the MSU can be replaced by a remote VN connected to the MSU by telemedicine (TM) thereby reducing manpower requirements and costs.

The successful completion of this project will provide data on important outcomes and costs associated with the use of MSU vs SM in the United States (U.S.) that will determine the value of integrating MSUs into the pre-hospital environment that would be more generalizable throughout the country. Therefore, the proposed study is the necessary step in a process that may dramatically modify the way that acute stroke patients are managed.

This is a prospective multicenter cohort study with randomized deployment weeks and blinded assessment of both trial entry and clinical outcomes.

2. DEFINITION OF TARGET POPULATION AND STUDY SAMPLES

2.1. Target Population

No. of Clinical Sites: 6
No. of subjects:

To be assessed for eligibility	(n = 4900)
To be enrolled	(n = 1845)
To be analyzed (“tPA eligible”)	(n = 1038)

Main criteria for inclusion:

1. Criteria for MSU team to **enroll** a patient into the study (to be determined pre-hospital on both MSU and SM weeks)

a. Last seen normal possibly within 4hr 30 min
b. History and physical/neurological examination consistent with acute stroke
c. No definite tPA exclusions per guidelines, prior to CT scan or baseline labs
d. Informed consent obtained from patient (if competent) or legal representative. Pre-hospital management and treatment, including IV tPA, will not be delayed for consent; however, consent in both MSU and SM patients must eventually be obtained for data to be retained for analysis.

2. Criteria for **tPA-eligibililty** (to be determined pre-hospital on MSU weeks, and after ED assessment on SM weeks, and confirmed by blinded adjudication)
   a. Meeting tPA inclusion and exclusion criteria per guidelines after CT scan, baseline labs, and clinical re-evaluation

2.2. Study Outcomes

2.2.1. Primary Outcomes

- The utility-weighted modified Rankin Scale (mRS) at 90 days, comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks.

2.2.2. Secondary Outcomes

- Comparing patients found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not) on MSU weeks compared to patients on SM weeks.
  - ordinal (shift) analysis of mRS at 90 days, and
  - proportion of patients achieving 90-day mRS 0,1 vs 2-6
  - 30% improvement from baseline to 24hr NIHSS

- The agreement between the VN on board the MSU with a VN remotely assessing a suspected stroke patient for treatment with tPA via TM in the MSU, and the rate of technical failures in conducting the TM consultation. N.B. Patients will include all enrolled patients on MSU weeks considered for tPA treatment.

- An exploratory cost-effectiveness analysis (CEA) of MSU versus SM using the Incremental Cost Effectiveness Ratio and Incremental Net Benefit estimate will be performed. N.B. The exploratory CEA will include all enrolled patients on MSU and SM weeks found eligible for tPA (based on a blinded review of the patient's chart, regardless of whether they were treated or not)

- Comparing all patients treated with tPA (whether or not adjudicated as tPA eligible) on MSU weeks compared to patients on SM weeks.
    - Utility-weighted modified Rankin Scale (mRS) at 90 days
    - ordinal (shift) analysis of mRS at 90 days, and
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS

- Comparing enrolled patients treated with tPA within 60 minutes of LSN onset according to published guidelines on either MSU or SM weeks, compared to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS) between the groups at the time of treatment. N.B. Patients will include only those patients actually treated with tPA based on the final determination of the time LSN, and will include only patients meeting all inclusion and exclusion criteria.
    - utility-weighted mRS at 90 days,
    - ordinal (shift) analysis of mRS at 90 days
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS
    - Instead of dichotomizing into two groups based on time from LSN to tPA, logistic regression of 90-day mRS 0,1 vs 2-6, using a restricted cubic spline for time from onset to treatment, with visualization of spline term compared with the odds ratio

- Comparing all patients treated with IAT (separate analyses for those adjudicated as tPA eligible, all tPA treated, or all IAT with or without tPA) on MSU weeks compared to patients on SM weeks.
    - utility-weighted mRS at 90 days
    - ordinal (shift) analysis of mRS at 90 days
    - proportion of patients achieving 90-day mRS 0,1 vs 2-6
    - 30% improvement from baseline to 24hr NIHSS

- The time from LSN to tPA treatment on all patients treated within 4.5 hours of LSN on MSU weeks compared to similarly eligible patients on SM weeks. N.B. Patients will include all enrolled patients actually treated with tPA (or on SM weeks, eligible for tPA treatment) meeting all inclusion and exclusion criteria, and based on the final determination of time of LSN. One analysis will compare the median times. A second analysis will also capture the patients who were eligible but did not receive tPA because it was too late, categorizing time into the following groups (e.g., 0-60min, 61-90min, 91min-180min, 181-270min, eligible but no tmt because>270).

- Of the enrolled patients that were eligible for treatment with tPA (according to

published guidelines) on MSU weeks compared to SM weeks, the percent that were treated within 4.5 hours and within 60 minutes of LSN.

- The time from LSN, from alarm time, and from ED arrival to start of endovascular procedure (intra-arterial thrombectomy-IAT) in patients who meet pre-specified criteria for IAT on MSU weeks compared to SM weeks. N.B. All patients receiving IAT will be included in this outcome.

- The proportion of all tPA-eligible patient having IAT on MSU weeks compared to SM weeks

- The median/mean time from LSN to tPA therapy decision on all patients considered for treatment within 4.5 hours of LSN on MSU weeks compared to SM weeks. N.B. Patients will include all enrolled patients meeting inclusion criteria whether or not treated with tPA.

- Time between 911 call and onset of etiology-specific BP management on MSU weeks compared to SM weeks. N.B. Patients will include all enrolled patients.

2.2.3. Safety Outcomes

- The incidence of symptomatic intracranial hemorrhage (sICH) in enrolled tPA treated patients on MSU weeks compared to SM weeks (Symptomatic intracranial hemorrhage defined as any intracranial blood accumulation associated with a clinical deterioration of $\geq$4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration) N.B. Patients will include all patients treated with tPA, whether or not they meet all inclusion and exclusion criteria.

- Mortality. N.B. All enrolled patients signing informed consent will be included in this endpoint and followed until 1 year.

- The incidence of stroke mimics and transient ischemic attacks (TIAs) in tPA-treated patients, and also in tPA-eligible patients, on MSU weeks compared to SM weeks. N.B. SM patients deemed eligible for tPA on their pre-hospital assessment who then completely recover by the time of arrival in the ED will equal the excess incidence of TIAs treated on the MSU pathway.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Randomization and Analytic Cohorts (The process is described in detail in the protocol)

Weeks when the MSU is available or not are randomly selected. Stroke events are orthogonal to whether the MSU was being deployed or not that week and thus participants will be randomly

entered into either the MSU or SM groups depending on when their stroke occurs.

The primary analytic cohort is based on a modified intention-to-treat (ITT) analysis where the subject will be assigned to the group that they were enrolled in (e.g. if a patient was enrolled using SM, they would be assigned to the SM group) and adjudicated (by the blinded adjudicator) to be tPA eligible. The usual ITT includes every subject who is randomized according to randomized treatment assignment. In this study, all patients within each group who are adjudicated as tPA eligible by an adjudicator blinded to group assignment are included. The randomized assignment is not conducted for each patient, rather we generally alternated weeks to be either MSU or SM weeks, which is independent of when a subject randomly has a stroke and calls 911. Therefore, this may be considered a cluster-randomized trial where the cluster is the days when the MSU is available and the other cluster is when MSU is not available. There is not anything clinically important to set the cluster of when the MSU was available or not as a week (e.g., an alternative design could set one week as having MWF as MSU days and TTH as SM days and the next week as the opposite), but this made it convenient to set work schedules and to have a similar amount of time dedicated to recruitment of MSU and SM subjects and there is not a scientific nor statistical rationale suggesting that the clusters would be related to the patient's outcomes and intervention effect. Patients are, in a sense, "randomly" allocated into the clusters based entirely on when they happen to have their stroke in relation to the prospectively determined cluster allotment of whether the MSU is available or not. Furthermore, in order to optimize the utilization of the MSU, some cities have 2 sites enrolling patients at the same time, with one site running the MSU and other enrolling SM patients and then they switch the next week.

There are a few cases when the MSU was not available during an "MSU week" (e.g. the unit is out of service on another call, had to be serviced for an oil change, staff were sick and therefore unable to come in) and stroke patients that were treated using standard management were enrolled into the study by the study team into the SM arm. These few subjects will be included in the primary analysis in the SM arm, but moved to the MSU arm in a sensitivity analysis (see section 5.1.3). The decision to include them in the primary analysis is based on a November, 2019 comparison of the SM subjects who were enrolled during an "MSU week" compared to the SM subjects enrolled during an "SM week". Baseline characteristics (age, sex, ethnicity, race, pre-stroke mRS, baseline NIHSS, tPA treatment, time from LSN to tPA bolus, endovascular treatment, and DTGP) were similar between the groups, confirming our belief that there should not be any added bias for including them in the primary analysis. The benefit of including them is to improve the MSU:SM ratio and to increase the chance of recruiting subjects according to the projected timeline. However, this analysis will be repeated at the end of the study to confirm that no significant differences exist between these two SM populations before including them in the MSU arm.

In response to peer review, post hoc analyses were added to look at two additional cohorts: (1) all enrolled, regardless of adjudication; (2) all adjudicated enrolled, excluding hemorrhages.

3.2. Blinding

Blinded assessment of both trial entry, tPA-eligibility, and study outcomes. All patients are screened for trial enrollment during their pre-hospital evaluation and management by the same investigators

on both MSU and SM weeks to ensure that comparisons are made between similar patients, using similar criteria, at a similar stage of illness. For enrolled patients, criteria for study enrollment and tPA treatment are subsequently reviewed by a vascular neurologist (VN) blinded to MSU vs SM assignment and not otherwise involved in study management or analysis. The blinded VN determines from a dedicated "adjudication form", omitting any time data or other information that would produce unblinding, if the patient meets criteria for study enrollment and for tPA treatment. For comparing outcomes between MSU and SM, we will only include tPA-eligible patients on both MSU and SM weeks, whether or not actually treated, based on this blinded review. Investigators obtaining all outcomes are blinded to treatment allocation.

3.3. Multiplicity

No adjustments for multiple comparisons will be made. However, the secondary analyses will be interpreted with caution.

4. SAMPLE SIZE DETERMINATION

4.1. Sample Size for the Phase III trial

The power of this trial was based on the difference in primary outcome, 90 d uw-mRS. Based on preliminary data, we expected 1.8 times as many MSU as SM patients because when we began the study, on SM weeks some patients were occasionally taken by EMS to non-participating stroke centers where they could not be enrolled into the study. On MSU weeks, these patients would be transported in the MSU only to participating hospitals and therefore enrolled. Subsequently, we have incorporated these non-participating hospitals into the study, thereby mitigating this gap and the groups are now balanced. With a sample size of 693 total tPA-eligible patients (446 MSU and 247 SM patients, assuming 10% lost to follow-up [LTF]), the study will have 80% power with a 0.05 Type I error to detect a difference between groups of 0.09 in the mean uw-mRS using a two-sample t-test. This difference is plausible and important. In a re-analysis of 11 acute stroke studies8, the difference in mean 90d uw-mRS between groups ranged from 0.024-0.25, with most positive trials in the range of 0.1. In the NINDS tPA trial, 90d uw-mRS difference was 0.09 between tPA and placebo.

In March, 2018, Dr. Grotta, blinded to study data, requested, and PCORI approved, an increased sample size to 1095 patients from the 693 initially requested, and to allow three additional sites to be added. This request was based on our reassessment of anticipated difference in 90 day uw-mRS based on a.) results of the Berlin non-randomized study which showed a 0.07 difference between MSU and control patients, b.) results of the DAWN trial which was the first completed study to use the uw-mRS, and c.) reanalysis of a substantial number of completed stroke trials where conventional mRS outcomes were translated to uw-mRS (see figure below). In that analysis, Broderick et al found that the smallest clinically meaningful difference was 0.04[1]. We based our initial sample size of 693 tPA eligible patients on the ability to detect a 0.09 point difference which was the same as between tPA and placebo in NINDS. The endovascular studies found a >0.10 point difference. Based on these pieces of information which were not available when we designed our study, Dr. Grotta reassessed

the anticipated difference between groups if the MSU produces a substantial reduction in time to treatment, and felt that a difference of 0.07 is a more realistic goal. Dr. Yamal did not participate in that decision since he is unblinded.

Assuming a 3:2 (1.5) imbalance, 5% LTFU, and using the pooled standard deviation of STEMO & No STEMO group (sd=0.385), numbers of patients needed to detect a difference of 0.07using a 2-sample t-test is N=1038. Our LTFU so far has been around 5% so we expect this assumption to be reasonable. PCORI has agreed to the increase in sample size and sites sufficient to detect a 0.07 difference.

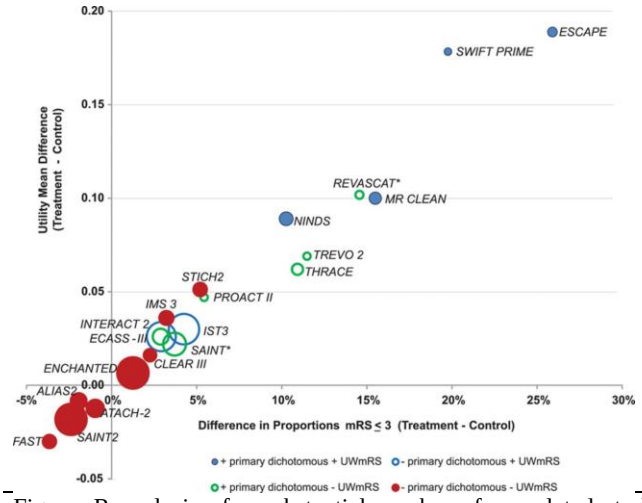

Figure. Reanalysis of a substantial number of completed stroke trials where conventional mRS outcomes were translated to uw-mRS. Effect sizes reported. From Broderick, et al.

4.2. **Sample Size Estimation for Cost Effectiveness Analysis**

We will perform an exploratory cost analysis using the cost data collected during this study. Based on the sample size estimation outlined in Willan et al[2], and cost and QALY estimations from past studies[3-6], we estimated a range of sample sizes that will be required for a formal CEA. The lowest and highest observed change in QALY in the literature was 5-20%; similarly observed change in cost was 10-25%. Based on these the sample size requirement in the most optimistic case was 96 patients (48 in each group) and in the most conservative case was 740 patients (370 in each group) for a power of 80% and p-value if 0.05. Approximately 50% of the patients for whom the MSU is dispatched, and who meet inclusion criteria for enrollment into the study, will receive tPA. Hence, the total number of patients used for the CEA will have to be between 192 and 1480 patients. Even though the current study probably will not meet the

sample size requirement for the conservative case, it will help establish the expected cost and QALY changes for the MSU intervention (which have never been estimated before).

5. ANALYSIS PLAN

5.1. Phase III Trial Analysis

5.1.1. Treatment Group Comparability at Baseline

Although the random enrollment of participants to the two treatment arms and blinded review of tPA eligibility should ensure comparability with respect to known and unknown variables, imbalance may occur by chance. Descriptive statistics for baseline characteristics known or suspected to be associated with outcomes will be prepared for the two treatment groups for all randomized as well as all deemed "eligible for tPA" based on the blinded review. Chi-square statistics and Wilcoxon rank sum tests will be used to evaluate baseline differences between the arms for categorical and continuous variables, respectively. Any variables with baseline differences will be included in secondary adjusted analyses. Also, completers will be compared to non-completers (loss to follow-up for 90 mRS) on these baseline variables to indicate whether missingness may be considered random.

5.1.2. Primary Clinical Analysis

The mean uw-mRS at 90d along with corresponding two-sided 95% confidence intervals will be compared between groups using a two-sample t-test or Wilcoxon rank sum test if the assumption of normality does not hold. Although the mRS is an ordinal outcome, the difference between the uw-mRS categories has clinical significance and the t-test assumption and central limit theorem are likely satisfied. The primary analysis of uw-mRS will be adjusted for baseline uw-mRS, site, any baseline covariates that are different between the two groups, and covariates associated with mRS, including baseline NIHSS, age, pre-morbid mRS, and previous TIA/stroke, in a linear regression model. If the assumptions of the model are not satisfied, a restricted cubic spline will be used to model baseline continuous variables (NIHSS and age). If the linear regression with splines does not fit well, we will use ordinal logistic regression to adjust for the variables. If the proportional odds assumption fails, we will use logistic regression with mRS 0-1 vs 2-6 as the primary analysis. Assuming that the primary analysis doesn't use the following models, sensitivity analyses of the primary outcome will be conducted including ordinal (shift) analysis using a proportional odds model and proportion achieving a dichotomized outcome of mRS 0-1 vs 2-6 using binary logistic regression.

In response to peer review, we added post-hoc propensity score analyses using propensity scores as an alternative way to reduce any effects of confounding to estimate the effect of MSU group on dichotomized mRS (0-1 versus 2-6). The individual propensities for enrolling into the MSU versus EMS groups were estimated using a separate selection multivariable logistic regression model with variables site, baseline NIHSS, pre-stroke

mRS, age, Black race, gender, and dichotomized time from LSN to EMS/MSU arrival (>1hr versus ≤1hr). Standardized mean differences were used to assess covariate balance before and after weighting (all standardized mean differences were < 0.1). The predicted probabilities were used to calculate stabilized inverse probability weights (IPW). The 90-day uw-mRS was further described using means and standard deviations and by fitting a univariate linear regression with outcome (90-day uw-mRS), covariate MSU group, and IPW according to the propensity score. IPW analyses of all enrolled patients was added post-hoc to assess the chances of post-enrollment selection bias and to align analysis with overall MSU vs EMS management with outcomes discharge mRS and 24hr NIHSS.

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Utility weights

The sample size was originally designed using the Dawn trial utility weights that were derived based on a United Kingdom sample and using the 3-level version of EQ5D. EQ5D-5L has been in use for more than a decade. However, the corresponding population-level utility weights for 5L had not been developed for many countries, and most countries only have population-level weights for the much older EQ5D-3L. In 2019 a study was published by Pickard et al. conducted a survey to develop utilities based on a US population and using the 5-level version of EQ5D (EQ5D-5L), which is more relevant to the participants in the BEST-MSU study. Using their Probit model estimated parameters to calculate utilities, in June 2020 we fit a linear regression model with these utilities (using 90-day EQ5D-5L) as the outcome and the 90-day mRS indicator variables as the independent variables to estimate our specific utility-weighted mRS. We also applied both the Dawn and the newly derived utility weights to the B-PROUD data and observed that results were consistent in the comparison of their mobile stroke unit data and their non-mobile stroke unit groups between these two weight choices. These were presented during the June 2020 study monitoring committee and were approved to use as the primary outcome of our trial. The weights based on the June 2020 data are presented in Table.

Table. Comparison of utility weights.

mRS	Dawn weights (previous MSU weights)	ENCHANTED trial weights	New proposed MSU
0	1	0.977	1
1	0.91	0.885	0.91
2	0.76	0.748	0.72
3	0.65	0.576	0.65
4	0.33	0.194	0.18
5	0	-0.174	0.05
6	0	0	0

5.1.3. Sensitivity Analysis of Primary Outcome

We will conduct sensitivity analyses using Dawn utility weights of the 90 day mRS. An additional sensitivity analysis will add an indicator of whether the SM subjects that were enrolled during an MSU week affect the treatment effect in a regression model by adding an indicator for these subjects. Also, in a sensitivity analysis, we will move these subjects into the MSU arm to check for consistency of results.

A further sensitivity analysis will remove subjects that were enrolled during the COVID-19 pandemic months (beginning of March, 2020).

5.1.4. Analyses of Ancillary Clinical Outcomes

We will also compare mRS at 90d (uw-mRS, Δ uw-mRS from baseline, ordinal (shift) analysis, and proportion achieving 0,1) in tPA treated patients treated within 60 minutes of LSN to patients treated 61-270 minutes, regardless of whether they were on MSU weeks vs. SM weeks. Patients on MSU weeks vs SM weeks will also be compared for differences in (a) the time from LSN to tPA treatment, (b) time from LSN, alarm time, and ED arrival to start of IAT, and for safety outcomes (i) mortality, (ii) symptomatic intracerebral hemorrhage, and (iii) incidence of tPA treated stroke mimics and transient ischemic attacks.

A logistic regression model will be used to compare 90 day mRS 0,1 vs 2-6 of patients treated with tPA within 60 minutes of symptom onset to similar patients treated 61-270 minutes after onset, adjusting for any imbalances in stroke severity (baseline NIHSS, age, premorbid mRS, and previous stroke/TIA incidence) between the groups at the time of treatment[8]. If baseline characteristics are significantly different between the two non-randomized groups, we will use propensity score analysis to limit potential bias. Also, we expect a higher incidence of spontaneous recovery (TIA) and stroke mimics may occur with earlier observation in the 0-60 minute group compared to those seen 61-270 minutes. The "natural history" of the incidence of spontaneous recovery and stroke mimics will be estimated from patients enrolled into the SM group, and will be considered in analyzing the comparison between patients treated with tPA within 0-60 min vs 61-270 min. Time to treatment and to endovascular procedures will be analyzed using Cox proportional hazards models, similarly to survival. Categorical outcomes will be analyzed using Fisher's exact test.

Unless there is sufficient power (predetermined before the analysis is begun) the approach to ancillary analysis will generally be the calculation of confidence limits on intervention group differences rather than formal tests of significance as the trial may not have high power to detect difference in all of these outcomes. However, these comparisons will add to the knowledge of the benefits and risks of the intervention.

5.1.5. Subgroup Analysis

Tests of effects within subgroups will be driven by clinical rationale. To reduce the potential for spurious results, we would test for a sub-group treatment interaction at a 0.2 critical level. Any subgroup analyses that are not pre-specified would be considered post hoc and reported as requiring confirmation in future studies. Estimates of the MSU effect will be obtained separately for pre-specified subgroups with significant treatment-by-subgroup interactions, using the methods described above. Pre-specified subgroups include (1) patients treated via TM versus on-site VN, (2) patients treated at various sites, (3) patients that had the EMS arrive (for SM) or MSU arrive (for MSU) within $\leq$1 hr and those that arrived >1hr of LSN, and (4) race. For (3), time will also be considered as a continuous variable and the interaction between time and MSU/SM will be assessed with transformations or restricted cubic splines of time used if appropriate).

When doing the TM subgroup analysis, we anticipate that there may be demographic differences between sites that are doing TM versus onboard VN. For this analysis we will conduct regression models, adjusting for baseline NIHSS, age, pre-morbid mRS, time since last seen normal, and previous TIA/stroke, in a linear regression model.

Analyses of post-randomization sub-groups are subject to many biases. Thus any analyses of post-randomization sub-groups, such as those treated with IAT, would be considered on a case by case basis requiring tailored use of advanced statistical methods[9] and careful interpretation.

5.1.6. Missing Data

We expect no missing data for baseline measures. For 90-day assessments, extensive efforts will be made to ascertain the modified Rankin scores and mortality status, though we anticipate a 5% rate of lost to follow-up. We will perform several approaches for handling missing data. Characteristics of patients who are lost to follow-up will be compared to those that remain in the study to assess the degree of any selection bias, and sensitivity analyses will be performed to evaluate robustness of conclusions to the different missing data approaches. We will use multiple imputation for the final values assuming missing at random, depending on if any significant baseline differences exist between those observations that have a missing value or not. As sensitivity analyses we will report the data with and without imputation. Data will also be stratified according to their missing pattern (e.g., early termination, late termination, and follow-up completers) and variables representing these groups will be used as model covariates in adjusted analyses.

5.2. Cost Effectiveness Assessment

5.2.1. Approach and Methods used in Cost Analysis.

In order to establish an economic basis for a higher reimbursement from the healthcare

payers for dispatching an MSU the following aspects have to be established:

- Does the MSU improve the post-discharge stroke severity and consequently improve average patient QALYs? Higher cost for an intervention can be better justified if associated with improved patient outcomes.
- Does the MSU reduce post-stroke healthcare utilization and consequently costs for the healthcare payers? Reduction of post-stroke healthcare utilization will subsequently save costs for the healthcare payers who pay for these utilizations. By identifying whether the healthcare payers save costs for stroke management due to the use of MSU (and determining the amount of post-stroke cost savings) the study can provide scientific evidence for supporting additional Medicare reimbursements for an MSU dispatch.
- What is the magnitude of the incremental fixed costs associated with MSU and the per-patient incremental fixed cost due the ambulance outfitting, CT, other equipment, and telemedicine technology, staffing requirements and paramedic training? Establishing the magnitude of incremental fixed cost per patient will help determine the justifiable amount of increased reimbursements to agencies operating the MSU and providers supporting its telemedicine capabilities.

5.2.2. Sample used for Cost Analysis

The cost-effectiveness analysis (CEA) will include all enrolled patients on MSU and SM weeks who meet criteria for tPA treatment whether or not they are eventually treated with tPA. We estimate that approximately 50% of enrolled patients will receive tPA in the MSU and SM group. The non-tPA treated patients will probably not benefit much from MSU management and since the primary goal of the MSU is to ensure quicker administration of tPA, only those patients who meet criteria to receive tPA will be included in the cost analysis (for one year cost and QALY follow-up). The cost of operating the MSU for the remaining 50% of the patients who are not eligible for tPA administration will be included as fixed costs of operating the MSU, but these patients will not be followed-up once they are deemed ineligible to receive tPA inside the MSU or at the ED.

5.2.3. Perspective of the cost-effectiveness analysis (CEA)

The CEA will be performed from the perspective of the healthcare payers. If dispatching an MSU improves patient outcomes it should theoretically reduce post-stroke healthcare utilization and hence the reimbursement costs for the healthcare payers under the current payment policies, which do not include additional reimbursement for an MSU dispatch. If the study demonstrates improved effectiveness along with cost-savings or demonstrates improved effectiveness with limited increase in costs for the healthcare payers it will help justify the additional reimbursements for dispatching an MSU. This justification is vital for the financial viability of this high cost intervention and hence critical for the study.

5.2.4. Measure of Effectiveness

Stroke results in severe morbidity, disability and mortality in the American population.23 More than 70% of the stroke patients are unable to return to their pre-stroke life style,

activities of daily living and employment. Thus, stroke has a permanent impact on the patient's QOL, thereby necessitating the use of a patient-centered effectiveness measure that considers both the quality and quantity of a patient's life, and is not limited to physician reported clinical measures or survival. Hence, QALYs will be used as the effectiveness measure. QALYs will be obtained through utility-weight conversions using the EuroQol's EQ-5D measure. ED-5D is preferred due to its standardized ease of conversion to QALYs.33,38 We considered the use of other QOL measures like Neuro-QoL. After communication with the Neuro-QoL research team it was established that Neuro-QoL has not been validated for conversion to QALYs. In addition, Neuro-QoL involves the reporting of 18 adult domains in the form of separate T-scores which should not be combined to form a single QOL measure further limiting the feasibility of QALY conversion. Since costs analysis requires QALYs and not QOL measures, Neuro-QoL and similar stroke-specific QOL measures, which cannot be converted to QALYs, are not used in this study.

5.2.5. Measure of Cost

The cost components include: 1) The incremental fixed costs associated with the MSU 2) The index hospitalization costs 3) The post-discharge cost during the first year after the stroke episode 4) Life-time costs after the first-year. The incremental fixed cost (component 1) for the MSU group will include cost of additional outfitting required to convert an ambulance into an MSU, cost of additional staffing changes for the agency operating the MSU, provider/hospital-level infrastructure changes to accommodate the MSU, clinical staff training, EMS and dispatch training, and all trips performed by the MSU (whether they involve tPA eligible patients or not). The variable cost (cost per patient) will include components 2 to 4, and will be measured for all patients in the MSU and SM group who meet criteria for tPA treatment whether or not they are eventually treated with tPA. Microcosting (resources * local market value) will be applied to the estimation of incremental fixed cost (component 1) whereas gross costing (utilization * Medicare payments) will be used for the variable costs of post-stroke healthcare utilization in the first year (components 2 and 3). Life-time costs after the first year (component 4) will be simulated using Markov modeling based on evidence from the literature[10,11]. The fixed cost of CT scanners and telemedicine equipment will be amortized over the 10 year expected life of the equipment. Medicare reimbursement amounts for patients from different geographic areas will be adjusted to make them nationally representative by using the CMS geographic adjustment factor (for part A claims) and CMS geographic practice cost index (for part B claims).

5.2.6. Funding and Cost Analyses

The cost analyses will not be supported by the PCORI funding.

6. MONITORING FOR EFFECTIVENESS AND SAFETY

6.1. Overview

Interim analyses for safety (symptomatic hemorrhage), efficacy/futility (dichotomized mRS 0-1 vs. 2-6), and process (time from alarm until treatment decision) will be conducted when the 90-day mRS has been collected on 50% of the total number of patients that are adjudicated to be tPA-eligible.

6.2. Interim Analyses for Effectiveness

The efficacy interim analysis of the 90 day dichotomized mRS will be a 2-sample, 2-sided test of proportions using a Haybittle-Peto boundary (p=0.001). This will be conducted on the subset that are tPA-eligible based on the blinded adjudication.

6.3. Interim Analyses for Futility

The futility analysis of the 90 day dichotomized mRS (0-1 vs 2-6) will be a 2-sample, 1-sided, test of proportions. The futility analysis will compare patients in MSU weeks vs SM weeks (alpha=0.15). If we reject the null hypothesis that the percentage of favorable outcomes (mRS<2) in patients in the MSU weeks is greater than or equal to the percentage of favorable outcomes in patients in the SM weeks plus 10%, we conclude that completing the trial would likely be futile. The futility hypotheses are: $H_0: p_{MSU} - p_{SM} \geq \Delta$ versus $H_A: p_{MSU} - p_{SM} < \Delta$ where p_{MSU} and p_{SM} are the proportions of participants expected to have a favorable mRS outcome in the MSU and SM groups, respectively, and Δ denotes the 10% increase in favorable outcomes over SM considered clinically meaningful. This will be conducted on the subset that are tPA-eligible based on the blinded adjudication.

6.4. Safety Analyses

Rates of symptomatic hemorrhage will be compared using a Fisher's exact test (alpha=0.05). This will be conducted on all enrolled tPA-treated patients, excluding any that had an ICH on their baseline CT scan.

6.5. Process Analysis

Time from alarm to treatment decision will be compared using a one-sided Wilcoxon rank sum test (alpha=0.05) to test if the time is longer for the MSU arm. This will be conducted on the subset that are tPA-eligible based on the blinded adjudication. MSU-by-site interaction terms will be included in a regression model to test if these differ by site and if the interactions are

significant then within-site tests will be conducted.

7. REPORTING PROCEDURES

7.1. CONSORT Diagram

We will account for every subject randomized into the study using a CONSORT diagram.

7.2. Primary Reporting for the BEST-MSU Study

We will account for every subject randomized into the study using a CONSORT diagram. Primary reporting for the BEST-MSU study will follow the classic CONSORT Checklist items (see appendix).

7.3. SMC Reports

Standard format for SMC reports will be developed and sent to the SMC for review before the initial safety analyses are presented, and the format will be added as an appendix to this report.

7.4. Publications

Before the BEST-MSU CCC begins an analysis for a manuscript or presentation, the first author or writing group will have their hypotheses and analysis plan reviewed and approved by a designated team at the BEST-MSU DCC.

8. REFERENCES

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Appendix A: CONSORT Checklist

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

http://jama.ama-assn.org/site/misc/auinst_chk.pdf