Blood Pressure after Endovascular Stroke Therapy (BEST)-II

National Clinical Trial (NCT) Identified Number: NCT04116112

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
9.1, 9.2, 9.3, 9.4	The statistical considerations portion is updated with the final statistical analysis plan. This includes the analysis of primary endpoints and safety analyses. .	The changes are made in compliance with recommendations from DSMB and based on interim analysis.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

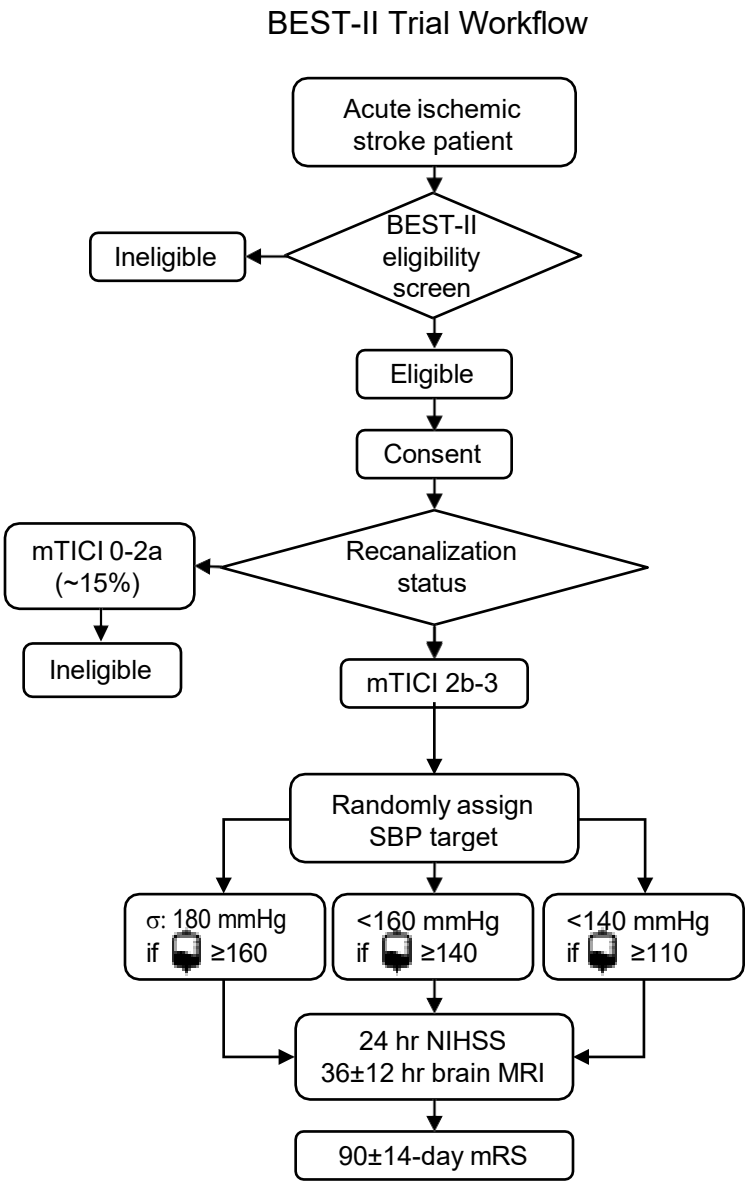
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will undergo review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Blood Pressure after Endovascular Stroke Therapy (BEST)- II
Study Description:	BEST-II is a prospective, randomized, open-label, blinded-endpoint (PROBE), clinical trial where eligible acute stroke patients will be randomly assigned (1:1:1) to one of the following systolic blood pressure targets: (1) a high target of ≯180mmHg (control), (2) an intermediate target of <160mmHg, and (3) a lower target of <140mmHg. The SBP will be maintained below the assigned target for 24 hours after a successful endovascular clot retrieval (EVT). In this stage, we will test the harm of the two intervention arms.
Objectives:	1) To assess the harm of lower SBP targets in successfully EVT-treated stroke patients by measuring effect on volume of brain infarct and patients' functional status. 2) To assess the probability of a successful future phase 3 trial
Endpoints:	Primary Endpoints: 1) Final infarct volume at 36±12 hours 2) Utility-weighted 90±14 -day modified Rankin Score Secondary Endpoints: 1) Any hemorrhagic transformation 2) Symptomatic hemorrhagic transformation 3) Neurological worsening associated with anti-hypertensive treatment 4) Follow-up MRI perfusion core and penumbra volumes.
Study Population:	We will include adult (≥18 years) patients undergoing successful EVT for an occlusion in the anterior cerebral circulation large vessel. A total of 120 will be randomized to one of the three SBP target strategies.
Phase:	2b
Description of Sites/Facilities Enrolling Participants:	Study patients will be enrolled at the Vanderbilt University Medical Center for the phase 2b. No centers outside of the US will participate in this study.
Description of Study Intervention:	Management of SBP will start immediately after satisfactory achievement of successful recanalization to lower and maintain SBP below the randomly assigned target for 24 hours. In the event where SBP values are above target, intravenous nicardipine will be initiated at 2.5 mg/hr to lower the SBP. If SBP is still not reduced to below assigned target after 15 minutes, nicardipine dose will be increased by 2.5 mg/hr every 15 minutes until the target SBP or a maximum dose of 15 mg/hr is reached.
Study Duration:	We project to complete enrollment of initial 120 patients over 36 months. Data analysis and study reporting will be completed within 12 months following the enrollment of the last patient.
Participant Duration:	90±14 days.

1.2 SCHEMA



: Treated with antihypertensive medication; mTICI: Modified Thrombolysis in Cerebral Ischemia; MRI: Magnetic Resonance Image; mRS: Modified Rankin Score; NIHSS: National Institute of Health Stroke Scale; SBP: Systolic Blood Pressure

1.3 SCHEDULE OF ACTIVITIES (SOA)

Schedule of Events						
	Prior to Enrollment	Enrollment	24 hours	36 (±12) hours	Day 7 or D/C (whichever first)	Day 90± 14
Screening & Eligibility	X					
Consent	X					
Randomization		#/X				
Medical History*		#				
Home Medications*	#					
Laboratory Studies*	#					
NIH stroke scale*	#		#			
Vital Signs*	#	#	#		#	
CT brain*	X		X			
CT Perfusion*	#					
CTA H&N*	X					
MRI (or CT) brain (FIV & Hemorrhage)*				X		
Nicardipine*			X			
Labetalol (if needed)*			X			
Discharge Summary*					X	
Adverse Events			X		X	
Serious Adverse Events			X		X	
Modified Rankin Score*						#
End of Study						X
*= Standard-of-Care; X = Manual task; # = Automated Task; D/C = Discharge; CTA H&N = CT Angiogram Head & Neck; FIV: Final Infarct Volume						

2 INTRODUCTION

2.1 STUDY RATIONALE

A quarter of all annual acute ischemic strokes (AIS) in the United States are caused by a large cerebral vessel occlusion (LVO).[1] They have the highest morbidity and mortality rates among all AIS etiologies.[1,2] Endovascular mechanical thrombectomy (EVT) is a revolutionary AIS treatment that rapidly and most efficiently removes the cause of the LVO, which is most often a blood clot. However, despite a successful recanalization with restoration of blood flow, about half of the EVT-treated patients remain disabled.[3]

Blood pressure (BP) after successful EVT-mediated recanalization is a readily modifiable parameter that may critically influence patient outcomes. The current guideline recommends maintaining systolic BP (SBP) 180 mmHg in the first 24 hours after EVT. This guideline permits higher than normal SBP without any robust evidence, including randomized studies.[24] While a higher SBP target may be necessary to improve or maintain perfusion, it may expose vulnerable ischemic brain tissue to hyper-perfusion injury and lead to oxidative stress, inflammation, and hemorrhage.[4-6] Conversely, lower SBP targets can minimize hyper-perfusion injury, but may compromise microcirculatory reperfusion and increase infarct volume.[7] In our recent multi-center prospective cohort study BEST-I and other preliminary work, SBP ≯160 mmHg in the first 24 hours after EVT correlated with worse functional outcomes.[8-11] In rodent models of transient LVO, lowering BP during the first 24 hours of reperfusion results in lower brain infarct volumes and incidences of hemorrhage.[12] We found considerable heterogeneity in the current practice of post-EVT BP management across United States in a recent survey,[13] with <140, <160, and ≤180 mmHg being the most commonly practiced SBP targets. These conflicting post-EVT BP management practice needs an urgent resolution to ensure optimal clinical care. Hence, large randomized studies are necessary to evaluate the efficacy of different post-EVT BP targets.[14,15] But first, due to legitimate concerns about potentially compromised perfusion and resultant worsening ischemia, safety assessments of these lower BP targets are obligatory prerequisites to larger efficacy trials.

2.2 BACKGROUND

2.2.1 Over half of endovascularly-treated stroke patients remain disabled at 90-days.
The financial burden of ischemic stroke is $40.1 billion annually in the United States and it will triple by the year 2035.[16] Strokes caused by a large vessel occlusion (LVO) contribute to the vast majority of ischemic stroke-related morbidity and mortality.[17] Endovascular mechanical thrombectomy (EVT) has revolutionized acute stroke treatment by unprecedentedly improving the outcomes of patients with LVO stroke.[3] Yet, over half of those treated with an EVT remain disabled at 90-days despite optimal patient selection and successful clot removal.[3] With increasing use of EVT for LVO stroke treatment,[18] measures to further improve outcomes of this devastating type of ischemic stroke is necessary. An important and possibly neuroprotective intervention is blood pressure (BP) management following EVT.

2.2.2 Post-EVT BP target may affect ischemic bed reperfusion
Higher systolic BP (SBP) after recanalization can lead to hyperperfusion. During reperfusion after transient LVO in rodent models, cerebral arteries demonstrate impaired in autoregulation and fail to maintain a constant cerebral blood flow over a wide range of systemic BP to prevent brain injury.[19,20] Increased SBP after successful EVT-mediated vessel recanalization following

removal of the obstruction causing an LVO can lead to hyper-perfusion injury resulting in inflammation, reactive oxygen species generation, and hemorrhage.[5] Conversely, lower SBP after recanalization may cause hypoperfusion, especially at the microcirculatory level,[7] and raise concerns for an increased infarct volume.[21,22]

2.2.3 Evidence of significant benefit in functional outcome with lower post-EVT SBP

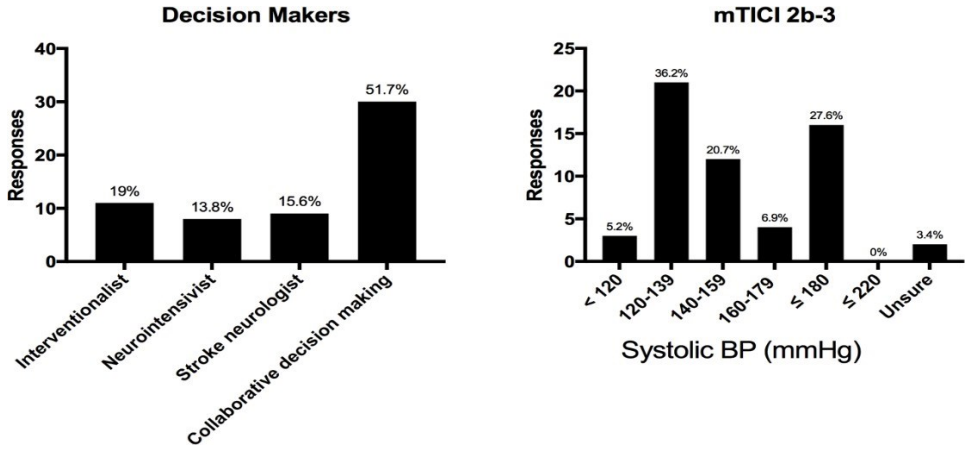
Table 1. Prior studies on association of Post-EVT Systolic Blood Pressure and Functional Outcome

Study	Year	No. of Patients	Study Variable	Outcome Measure	OR with 95% CI
Mistry et al.	2017	228	Peak SBP (continuous decrement)	mRS shift towards worse outcome	0.98 (0.97, 1.0)
Goyal et al.	2017	217	Peak SBP (10 mmHg decrement)	mRS 3-6	0.70 (0.56, 0.87)
Maier et al.	2018	168	Peak SBP (continuous decrement)	mRS 3-6	0.96 (0.93, 0.99)
Mistry et al.	2019	485	Peak SBP</=158 mmHg	mRS 3-6	0.77 (0.48, 1.23)

Prior observational studies[8-11] (Table 1) have shown that lower SBP in first 24 hours after EVT is associated with lower likelihood to bad functional outcomes, defined as functional dependence or death at 90 days (score of 3-6 on modified Rankin scale). Specifically, patients had worse outcomes if their SBP was higher than 160 mmHg following EVT.

2.2.3 Current landscape and scope of post-EVT BP management practice

The 2018 American Heart/American Stroke Association guidelines recommend lowering SBP to ::180 mmHg in the first 24 hours after an EVT.[23] These guidelines allow for a higher than normal SBP but are not supported with robust evidence. No randomized clinical trial has been conducted in patients treated with EVT to establish the efficacy of permissive hypertension (≤180 mmHg) over lower SBP targets. Not surprisingly, we found in our survey of 51 comprehensive stroke centers across the US that the current SBP management practice is quite heterogenous and deviates widely from these guidelines.[13] The post-EVT BP target is an



individualized decision taken collectively by a team of clinicians involved in each patient's care. There is a lack of expert consensus on the ideal post-EVT BP target (Figure 1).

Figure 1. Results of StrokeNET Survey of 51 Sites. A) Who decides the post endovascular therapy (EVT) blood pressure (BP) target? B) What is the target systolic BP post-EVT in patients with successful recanalization?

2.2.4 Urgent need for a randomized trial on optimal post-EVT BP target

Evidence based resolution to this anecdotal practice is urgently needed and asserted by the 2018 AHA/ASA guideline committee and leaders of the Stroke Treatment Academic Industry Roundtable as a premier question in stroke that needs an urgent answer.[14,15,23] Large randomized studies are necessary to evaluate the efficacy of different post-EVT BP targets. Optimization of post-EVT BP management may not only improve patient outcomes but also standardize all future EVT-related research.

2.2.5 Safety of post-EVT BP management with lower targets remain unestablished.

Pre-clinical studies in rodent models have shown that antihypertensive treatment with BP reduction following a transient LVO results in smaller infarcts and lower rates of hemorrhage.[12] However, safety of BP management strategies aimed at lowering SBP and their effects on brain perfusion remain unestablished in humans. Therefore, due to a potential for compromised perfusion and resultant worsening ischemia, safety assessments of these lower SBP targets are required prior to a larger efficacy trial.

2.2.6 Choice of post-EVT SBP targets

Targeting post-EVT SBP ≤180 mmHg is the current standard of care and recommended by the guidelines. Our prospective multi-center observational study, BEST-I,[11] was specifically designed to unveil the threshold of post-EVT SBP that best dichotomizes outcomes in EVT-treated patients for testing in a randomized trial such as the BEST-II. This study identified that a peak post-EVT SBP of 158 mmHg, for practical purposes 160 mmHg, best dichotomizes these outcomes. In a nationwide survey,[13] we found that most commonly practice post-EVT SBP targets were the following: <140 (41%), <160 (21%), and 180 (35%). To capture these most commonly utilized post-EVT targets, the BEST-II trial will randomly assign patients to one of these three SBP target arms.

2.2.7 Choice of antihypertensive agent

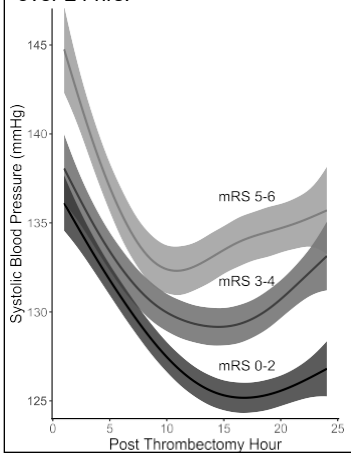
Intravenous nicardipine is the most commonly used antihypertensive agent across the US institutions to control post-EVT BP. As noted in our survey, 74% of the US institutions use nicardipine infusion as the first line agent followed by labetalol, which is used in 16% institutions. Both these medications have undergone testing for BP reduction in other acute cerebrovascular conditions (e.g the ATACH-2 trial and acute stroke trials) and are deemed safe and feasible agents. Additionally, both these agents are readily available across the institutions in the US and allow a stringent BP control with easy titration. Thus, BEST-II will utilize nicardipine as the first line and labetalol as the second line agent for BP reduction post-EVT.

2.2.8 Timing and duration of initiating antihypertensive management

Our preliminary observational data suggests that antihypertensive management should begin immediately after recanalization. During the LVO, there is often a physiological increase in BP to attempt to maintain brain perfusion. After a successful recanalization with an EVT, a physiological

decline in SBP seen in most patients. In BEST-I, patients with who died or lived with severe disability (mRS 5-6) had on average the highest SBP throughout the 24 hrs. In patients who had a moderate disability (mRS 3-4), the physiological decline of SBP failed to persist throughout the 24 hrs, often rising during the latter aspect of the 24 hrs, unlike those who had favorable outcomes (mRS 0-2) (Figure 2).

Figure 2. Time dependent changes in the SBP according to 90-day patient outcome in BEST-I. Lines with the ribbon represent a fitted generalized additive model (mean-like) with 95% confidence Interval of all (>17,000) SBP values recorded over 24 hrs.



2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks associated with endovascular mechanical thrombectomy: As a part of their clinical care, adult patients with anterior LVO stroke undergoing EVT are at a risk for death, coma, altered mental status requiring endotracheal intubation, bleeding in the brain and/or groin, vessel injury, vessel re-occlusion, further strokes, malignant cerebral edema, infection, condition that require surgical treatment, and long-term cognitive dysfunction among several possibilities.

Risks associated with higher SBP target: Higher SBP may lead to hyperperfusion brain injury and hemorrhage in stroke patients treated with EVT. This may clinically manifest as a neurological decline. Normally, cerebral arteries have the unique autoregulatory capability to maintain a constant cerebral blood flow over a wide range of systemic BPs to prevent brain injury. During recanalization after transient LVO in rodent models, cerebral arteries demonstrate impaired autoregulation, leading to increased blood flow in response to increased BP.[20,21] Although high SBP values associated with worse outcomes in EVT-treated stroke patients in preliminary data, a causal relationship remains to be established with a high-level of evidence.

Risks associated with lower SBP targets: Lower SBP may compromise reperfusion, especially at a microcirculatory level, and worsen ischemia in stroke patients treated with EVT. Additionally, chronically hypertensive patients may experience systemic complications from targeting lower SBP, for example, kidney hypoperfusion. Although lower SBP associated with better outcomes in EVT-treated stroke patients in preliminary data, a causal relationship remains to be established with a high-level of evidence.

Risk associated with selection of SBP target by the study: The above risks are experienced by EVT-treated stroke patients randomized to higher or lower SBP targets as part of routine care and outside of the context of clinical research. Currently, an ideal post-EVT SBP target from both safety and efficacy standpoint is unknown. SBP targets are currently selected anecdotally. In BEST-II, the target of SBP will be decided randomly by the study. To ensure that this randomly selected target does not pose additional risk to the patient compared to what would have selected by a practitioner in routine care, if a treating practitioner feels a specific SBP target other than that randomly assigned to the patient is required for safe treatment, the SBP target for that patient may be modified using a one-page “Target Modification Form”. The

BEST-II trial will only control choice of SBP target when the perceived risk associated with each randomly assigned target for an individual patient is equivalent in the treating practitioner's opinion. Any risks (or benefits) associated with each target may be enhanced in the trial setting due to higher adherence compared to routine care.

Risks associated with collection of protected health information (PHI): Collection of PHI for research involves a small risk for violation of patient confidentiality. To minimize this risk, only the minimum amount of PHI needed to conduct the study will be collected. All data collected will be generated during clinical care, and no additional data will be collected for research. At no time will we reveal subject identities in any manner, including research presentation, descriptions, or publications. All data will be entered into a secure, password-protected REDCap database. All patients will be assigned a unique patient identifier upon enrollment in the study. Patient identifiers will only be accessible to the PI and a select few research staff. Once the study results have been published, all study records will be stripped of any PHI in order to maximize patient and surrogate confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

The proposed trial is urgent. Thousands of patients undergo EVT every year in the US, yet, sparse evidence exists to guide post-EVT BP management. The primary benefit from the proposed research is the generation of data of the highest quality for the safety of mostly commonly practiced BP managements to inform the optimal BP management approach in EVT-treated patients. Results of BEST-II are necessary for the design of larger efficacy trials to improve outcomes in half of the successfully EVT-treated acute ischemic stroke patients that remain disabled. Even a small improvement in mortality and disability of these patients could translate into a great reduction in stroke-related societal economic burden. The findings of this study will also significantly improve our understanding of safety, efficacy, and mechanistic effects of different post-EVT BP strategies that are all within scope of current practice.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Every patient in the proposed research would have otherwise been assigned an SBP target without clear evidence for safety or efficacy. Patients participating in the trial may benefit from participation, to the extent that adherence to one of the assigned SBP targets improves outcomes or avoids harm. The minimal risks associated with transferring the selection of the SBP target from the treating clinician to the study and violation of confidentiality are greatly outweighed by potential improvement in clinical care provided by the research.

The BEST-II trial is a necessary step towards a larger efficacy trial to generate rigorous evidence for optimal post-EVT BP management strategy. With this overarching goal, the BEST series of studies will standardize future EVT-related research and translate into improved outcomes of numerous EVT-treated acute ischemic stroke patients who still remain disabled despite receiving the best treatment currently possible.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the harm of lower SBP targets in AIS patients that are successfully treated with EVT. To assess the probability of a positive phase-III trial evaluating the efficacy of lower SBP targets at improving functional outcomes of EVT-treated patients	1) Infarct volume on 36 +/-12 hr MRI (or CT scan if MRI contraindicated) 2) 90±14 -day Utility-weighted mRS (UW-mRS) with following utility weights: mRS 0 - 1.0; mRS 1 - 0.91; mRS 2 - 0.76; mRS 3 - 0.65; mRS 4 - 0.33; mRS 5 - 0; mRS 6 – 0.	Concern for potential compromised blood flow to the ischemic brain tissue and resulting increase the infarct volume and worse functional outcome is the primary safety concern for clinicians when targeting lower SBP in post-EVT patients. The multiple-primary endpoints are chosen to mechanistically establish safety of lower BP targets after a successful EVT. Additionally, preliminary evaluation of efficacy will be performed using the 90±14 -day UW-mRS endpoint. To evaluate the efficacy of lower SBP targets at improving functional status of the patient, trial simulations will be performed using the patient-centered UW-mRS as primary endpoint after taking the observed effect and remaining uncertainty.
Secondary		
To evaluate the effects of SBP targets on intracerebral hemorrhage, neurological worsening, and brain perfusion.	1) Any intracerebral hemorrhage on 36 +/- 12 hr MRI/CT 2) Symptomatic intracerebral hemorrhage on 36 +/- 12 hr MRI/CT	To evaluate the effect of BP targets on brain perfusion, we will evaluate incidence of any and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	3) Neurological worsening associated with anti-hypertensive treatment	symptomatic intracerebral hemorrhage (measures of hyperperfusion) as well as follow up MRI (or CT) infarct volumes (to estimate hypoperfusion). We will also evaluate the frequency of neurological worsening associated with antihypertensive agent to estimate immediate safety concerns with BP lowering in the post-EVT setting.
Feasibility & Compliance		
To determine the feasibility and compliance of maintaining SBP below the randomly assigned target in EVT-treated patients	1) Compliance Outcome – Hourly maximum SBP above target from 2-24 hours post treatment initiation 2) Feasibility Outcome – Separation of hourly maximum SBP values between three SBP target groups 2-24 hours after treatment initiation	Compliance outcome is defined as such to avoid mislabeling spontaneous drops in SBP as non-compliance.

4 STUDY DESIGN

4.1 OVERALL DESIGN

BEST-II is a prospective, randomized, open-label, blinded-endpoint (PROBE), clinical trial, in which eligible acute stroke patients will be randomly assigned (1:1:1) to one of the following systolic blood pressure targets: (1) a high target of ::180mmHg (control), (2) an intermediate target of <160mmHg, and (3) a lower target of <140mmHg. The SBP will be maintained below the assigned target for 24 hours after a successful endovascular clot retrieval (EVT). We will test the harm and efficacy of two intervention arms.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The first stage of the BEST-II trial is designed to test null hypothesis of "no harm" and an alternative hypothesis of "harm" of lower SBP targets. Failure to reject null hypothesis (one tailed p>0.05) will establish a lack of evidence of "harm". Thus, BEST-II paradoxically assesses safety by directly testing for harm. In other words, we will detect a "lack of evidence of harm" rather than "evidence of no harm".

4.3 JUSTIFICATION FOR DOSE

Please refer to section 2.2.6.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the 90±14 -day follow-up shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female adult patients (≥ 18 years)
2. Undergoing successful EVT (defined as mTICI ≥2b) for an occlusion in the anterior cerebral circulation large vessel (specifically, internal carotid artery and M1 or M2 segments of the middle cerebral artery).

5.2 EXCLUSION CRITERIA

We will exclude patients with comorbid conditions that may require condition-specific BP management such as those with 1) a diagnosis of heart failure with ejection fraction <30%, 2) left ventricular assist device, and 3) extracorporeal membrane oxygenation. Additionally, pregnant women and patients enrolled in other clinical trials will also be excluded.

5.3 LIFESTYLE CONSIDERATIONS

Not Applicable

5.4 SCREEN FAILURES

Screen failures will be defined as participants who consent to participate in the BEST-II trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of information on demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) will be recorded for these patients.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an initial inability to undergo EVT may be rescreened if this decision is revoked. Rescreened participants will be assigned the same participant number as for the initial screening.

Of the patients meeting inclusion criteria without meeting the exclusion criteria will have an opportunity to participate in the study. Of these, a total of 120 with successful recanalization (defined as an angiographic score of 2b or 3 on the modified Thrombolysis in Cerebral Ischemia scale, or mTICI) will be randomized to one of the three SBP target strategies. Patients in whom a successful recanalization is not achieved will be followed but not intervened upon. These patients will not be considered screen failures.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will enroll 120 patients with successful EVT of their anterior cerebral circulation large vessel stroke in BEST-II at Vanderbilt University Medical Center, with an anticipated accrual rate of 3.3 patients per month. No other site will participate or enroll patients in this trial. To reach this parget sample size, we anticipate screening about 300 patients during the study period of 36 months. We will not select patients based on gender, race, or ethnicity. The anticipated demographics are presented in the table below.

Table. Gender and race/ethnicity of EVT-treated stroke patients since 2012 at Vanderbilt University Medical Center.

Male	Female	White	Black or African American	Asian	Native Hawaiian or other Pacific Islander	American Indian/Alaska Native	Hispanic
50.1%	49.9%	83.4	12.5%	1%	<1%	<1%	4.1%

Enrollment will commence after receiving Institutional Review Board approval for human subject research. All stroke patients amenable to EVT at Vanderbilt present to the emergency room prior to being transported to the angiography suite for intervention. Patients will be screened in the emergency room or the angiography suite for eligibility using the study inclusion/exclusion criteria by a stroke physician, neuro-interventionist, or study coordinator. Upon meeting enrollment criteria, a consent will be obtained electronically using REDCap from the patients or their legally authorized representative. The electronic consenting process allows the consenting party and study personnel to be on or off site, which is critical given the acute time-frame in which stroke patients are treated. Capacity of a potential study subject will be determined by a trained study personnel based on the ability to communicate, understand, and ask questions. Once consent is obtained, patient will be randomized to one of the three systolic blood pressure target groups after satisfactorily successful recanalization is achieved, defined as mTICI ≥2b. Study intervention will begin soon after randomization. Members of the study team will be available to answer any questions during recruitment process and during the study period.

All consecutive stroke patients presenting to Vanderbilt University Medical Center who meet inclusion criteria without meeting exclusion criteria will have an opportunity to participate in this study. At Vanderbilt University Medical Center, 90-day follow-up with modified Rankin score is obtained via a phone interview by the stroke coordinator with a 90% success rate. We have conservatively accounted for a 15% loss to follow-up for this 90-day clinical primary outcome. We will ensure that contact information for the patient and legally authorized representative is

documented within patient's electronic medical record system and electronic consent form to minimize loss to 90-day follow-up. A 36±12-hr post-EVT MRI scan is performed in all EVT-treated stroke patients (unless contraindicated, in which case a CT scan is performed). All EVT-treated patients, thus, have either MRI or CT scan as routine care at 36±12 hours. We do not foresee any loss to follow-up for this radiographic primary outcome.

By the nature of the condition, a considerable portion of patients with acute LVO experience acute cognitive dysfunction. They are a vulnerable population. Inclusion of these patients is required to inform an optimal BP strategy for all patients undergoing EVT. Exclusion of all patients with cognitive impairment at the time of enrollment will result in a study population that is not representative of EVT-treated stroke patients in usual practice. Our institution and research team have an extensive experience in undertaking investigations that involve vulnerable patients, and we will apply our expertise in minimizing risks for these study participants. Other special populations, such as fetuses, neonates, pregnant women, children, and prisoners will not be eligible for inclusion

Participants will not be compensated in any form for their participation in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Management of SBP will start after randomization to lower and maintain SBP below the assigned target for 24 hours. In the event where SBP values are above target, intravenous nicardipine will be initiated at 2.5 mg/hr to lower the SBP. If SBP is still not reduced to below assigned target after 15 minutes, nicardipine dose will be increased by 2.5 mg/hr every 15 minutes until the target SBP or a maximum dose of 15 mg/hr is reached.

6.1.2 DOSING AND ADMINISTRATION

In the event where SBP values are above the randomly assigned target, intravenous nicardipine will be initiated at 2.5 mg/hr to lower the SBP. If SBP is still not reduced to below assigned target after 15 minutes, nicardipine dose will be increased by 2.5 mg/hr every 15 minutes until the target SBP or a maximum dose of 15 mg/hr is reached.

If SBP is above target despite maximum nicardipine infusion for 30 minutes, 10-20 mg of intravenous labetalol will be added every 15 minutes. If SBP remains unresponsive for 1 hr despite the use of maximum doses of nicardipine and labetalol, a third agent, Hydralazine, will be added at the treating physician's discretion. Incidence of the latter scenario is anticipated to be exceedingly rare.

We will only target peak SBP as spontaneous SBP reductions are expected after successful recanalization. However, if anti-hypertensive medication is used to lower the SBP then we will obey the following protocol. In the high target group, if the SBP falls below 160 mmHg, nicardipine will be titrated down until it returns within 160-180 mmHg or nicardipine is

discontinued. If the SBP falls below 140 mmHg in the lower target group of <160mmHg or below 110 mmHg in lower target group of <140, nicardipine will be titrated down until it returns within 140-159 and 110-139, respectively, or nicardipine is discontinued. Attempts to increase the SBP will only be made at the discretion of the attending physician (e.g. associated neurologic worsening).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Both nicardipine and labetalol are routinely used in the Neurological ICU as standard-of-care for BP management and are readily available in the central pharmacy and medication dispensing system.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not Applicable.

6.2.3 PRODUCT STORAGE AND STABILITY

Nicardipine and labetalol will be stored per Vanderbilt University Medical Center Pharmacy protocols.

6.2.4 PREPARATION

Nicardipine and labetalol will be prepared and dispensed per Vanderbilt University Medical Center Pharmacy protocols.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization: Enrolled patients will be randomized (1:1:1; stratified permuted block randomization) after the achievement of recanalization while in the angiography suite using REDCap randomization tool integrated within EHR, to one of the following groups where SBP will be lowered and maintained for 24 hours after a successful EVT: (1) High SBP target (::180mmHg; standard-of-care), (2) Lower SBP target (<160mmHg; intervention), and (3) Lower SBP target (<140mmHg; intervention).

Blinding: Given the nature of the experiment, the treating neuro-intensivist and other neuro-ICU staff will not be blinded to the treatment group assignment. Imaging outcome assessment will be performed by a central blinded imaging reader with an adjudication by a blinded neuroradiologist. A blinded stroke coordinator will assess clinical outcomes.

6.4 STUDY INTERVENTION COMPLIANCE

SBP Monitoring: BP will be monitored in a recumbent position using a BP cuff with the following frequency: Every 5 minutes for the first 15 minutes following nicardipine initiation or dose adjustment, then every 15 minutes for the 1st hr, followed by at least every 30 minutes until the end of 24 total hours after EVT. Arterial line and more frequent BP measurements will not be required but may be used by the treating physician based on medical indication.

Feedback on SBP Compliance: Study personnel will remotely monitor SBP values in real-time 8am-5pm Monday through Friday. 10% of the hours during nights and weekends will also be monitored. Real-time monitoring will aid identification of any lags between out-of-range SBP values and nicardipine titration and provision of timely feedback to nurses and ICU staff. This will allow us to identify barriers to SBP target compliance. Study personnel will regularly attend unit, nursing, and physician meetings to educate clinical personnel, solicit safety concerns, and address barriers to SBP target compliance.

6.5 CONCOMITANT THERAPY

Not Applicable.

7 DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If at any point during the treatment period of 24 hours following EVT the treating clinician feels that the SBP target should be different from that of the randomly assigned target for patient safety, the target will be modified to what is judged best by the treating clinician. These scenarios can include but are not limited to the following: 1) Neurologic deterioration associated with anti-hypertensive treatment or permissive hypertension 2) Follow-up radiographic findings (e.g. intracerebral hemorrhage on CT scan) requiring more stringent BP control 3) Vessel re-occlusion requiring more liberal BP control. These findings will be reported as AE or SAEs.

This can be done using a one-page “Target Modification Form” outlining the rationale for modification, new SBP target, and any additional comments. No re-challenge of the randomly assigned SBP target intervention will be made. These patients will complete all study activities including the standard of care 90±14 -day follow-up per the study protocol. All efforts will be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems (UPs).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants will have the right to voluntarily withdraw from participation in the study at any time upon request. An investigator may discontinue the study intervention for the following reasons:

- Pregnancy diagnosed after enrollment
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for >1.5 hours following successful recanalization.

The reason for participant discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up for the primary end-point of UW-mRS if he or she is unable to be contacted by the study site staff, either via a telephone or an in-person meeting at 90± 14-days after randomization. A participant will be considered lost to follow-up for the primary end-point of infarct volume if neither MRI or CT scan is obtained at 36 ± 12 hours following randomization. The latter scenario is expected to never occur during the study as obtaining a follow-up brain imaging in form or either MRI or CT is not only standard of care but also best medical practice.

Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Primary endpoints assessment:

1) 90±14 -day Utility-weighted modified Rankin score: An attempt to obtain a modified Rankin score is obtained at 90±14 days after the day of admission is made for all stroke patients admitted to the Vanderbilt University Medical Center. This attempt is made by the stroke-coordinator via a phone call or clinic follow-up. The stroke coordinator will be blinded to the SBP target assignment. The modified Rankin score (mRS) is an ordinal disability score ranging from 0 (no symptoms) to 6 (death). Utility weights are assigned to this ordinal scale for practical applicability since the difference between any two points on the scale is not linearly proportional to the difference in 'value' placed by humans to their corresponding levels of disability. Thus, to make this scoring system more patient-centered, utility weights will be assigned as follows- mRS 0 - 1.0; mRS 1 - 0.91; mRS 2 - 0.76; mRS 3 - 0.65; mRS 4 - 0.33; mRS 5 - 0; mRS 6 – 0

2) Infarct volume on 36 (±12)-hr MRI or CT scan (FIV): At 36±12-hours post randomization, patients undergo an MRI scan with at least DWI, T2 FLAIR, and GRE or SWAN sequences as standard-of-care. In case of contraindication to an MRI, a 36-hour CT scan will be obtained. The infarct volume will be manually calculated by a blinded imaging reader and will be adjudicated by a blinded neuroradiologist.

Other assessments for BEST-II include radiographic, physical, and questionnaire type evaluations outlined below:

- **Radiographic or other imaging assessments**.
  In addition to the FIV, the following imaging endpoints will be assessed:
  1) Baseline CT scan (standard-of-care): ASPECT score determined by the reading radiologist and extracted from the radiology report.
  2) Baseline CT angiogram (standard-of-care): Location of the large vessel occlusion determined by the reading radiologist and extracted from the radiology report and modified Tan collateral grade determined by a trained personnel as part of the study procedure.
  3) Baseline CT perfusion (standard-of-care): CTP will be processed using the iSchemaview RAPID software to automatically determine the core and penumbra volumes as well as the hypoperfusion intensity ratio (HIR; used to assess collateral circulation) which will be extracted.
  4) 36 (±12)-hr MRI or CT scan (standard-of-care): Presence or absence of hemorrhage will be determined by the reading radiologist and extracted from the radiology report. In case of contraindication to an MRI, a 36-hr CT scan will be obtained.
- **Physical examination**. NIH stroke scale will be calculated at baseline and 24 hours by trained personnel. Patients will be closely monitored in the Neurological ICU during the study procedure and any changes in the neurological examination will be rapidly identified by the ICU staff.
- **Laboratory evaluations**. Baseline standard-of-care laboratory values of glucose, platelet, International Normalized Ratio, Blood Urea Nitrogen, and creatinine will be recorded. 36 (±12) hr Blood Urea Nitrogen and creatinine will be obtained as standard-of-care.
- **Administration of questionnaires or other instruments.** Baseline modified Rankin score will be obtained when possible by trained personnel prior to EVT.
- **Other clinical care during 24 hours of the study period and all clinical care after 24 hours** will be provided according to the American Heart Association/ American Stroke Association guidelines.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) will be any untoward medical occurrence for a patient enrolled in BEST-II, regardless of whether the event was considered intervention-related or not. Events tracked as clinical outcomes are not considered adverse events.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

AEs that meet any of the following criteria will be considered Serious AEs (SAEs):

a) Results in death

b) Is life-threatening (defined as an event in which the participant was at risk of death at the time of event and NOT an event that hypothetically might have caused death if it would have been more severe)
c) Prolongs existing hospitalization
d) Results in persistent or significant disability above and beyond what would be expected for the underlying ischemic stroke.
e) Results in a congenital anomaly or birth defect
f) Medical event that requires intervention to prevent any of the above a-e.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.2.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the literature for SBP lowering in acute cerebrovascular conditions.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Study personnel will monitor enrolled patients for AEs throughout the trial and follow all AEs until they are resolved. All AEs will be recorded on the electronic case report form (eCRF). Information on event description, time of onset, clinician's assessment of severity, relationship to intervention, and time of resolution/stabilization of the event will be collected.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

Study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

8.2.5 ADVERSE EVENT REPORTING

All AEs will be recorded in the eCRF and communicated to the PI within 5 days. PI will in turn report all AEs to the Institutional Review Board (IRB) and DSMB as part of annual review process as required.

The BEST-II trial will monitor, track, and report all Clinical Outcomes and AEs as required by regulatory bodies.

Clinical Outcomes (not considered Adverse Events): Stroke-related mortality, disability, and intracranial hemorrhage are expected clinical outcomes for patients included in this study and will be tracked and collected as a study outcome on the eCRF and will be included in the statistical analysis. For reporting purposes, events listed below will not be reported as AEs unless believed to be study related or more severe or prolonged than expected given the underlying stroke.

1. Death (all deaths occurring prior to discharge be reported in the eCRF).
2. Intraparenchymal intracranial hemorrhage without or without receipt of surgical or medical intervention.
3. Neurological decline within 24 hours post-treatment initiation (defined as 4 points of more increase in NIH stroke scale)
4. Disability scored on the modified Rankin scale at 90±14 - days post-stroke.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the PI within 72 hours and the PI will report to IRB, DSMB, and NINDS no later than 7 days of occurrence.

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related and will include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (listed in 8.2.5) will be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event. In that case, the PI will immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the IRB/DSMB/NINDS and will be provided as soon as possible.

8.2.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed about AEs and SAEs, and study-related results on an individual level via an in-person visit prior to discharge or a telephone call after discharge from the Vanderbilt University Medical Center.

8.2.8 EVENTS OF SPECIAL INTEREST

Not Applicable

8.2.9 REPORTING OF PREGNANCY

Not Applicable

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems are those that involve risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2 UNANTICIPATED PROBLEM REPORTING

The principal investigator will report unanticipated problems (UPs) to the Vanderbilt Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 30 days of the investigator becoming aware of the problem.

8.3.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not Applicable

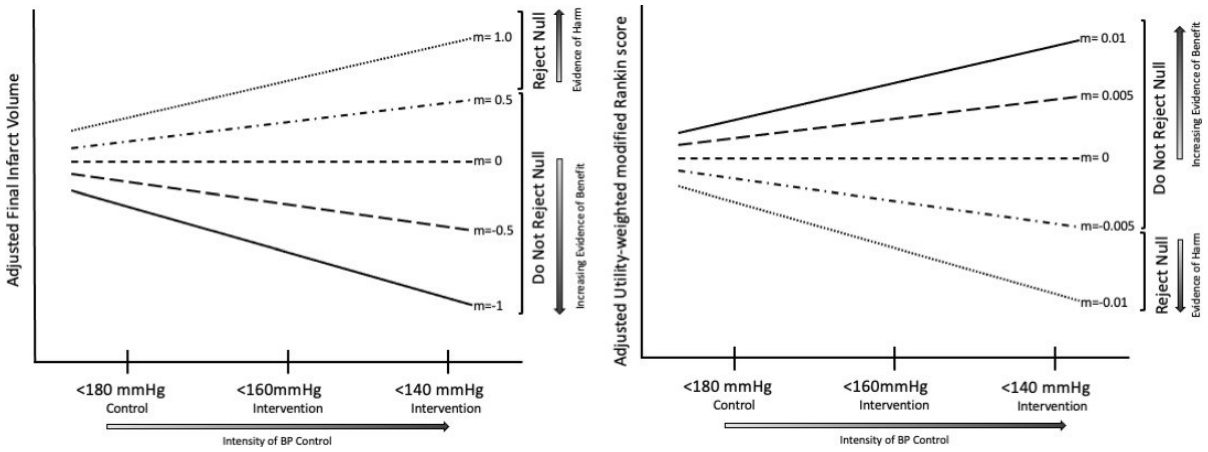
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Hypothesis 1: A 10 cubic centimeter (cc) increase in the FIV is considered clinically meaningful and known to be associated with worse outcome. A 10 cc increase in FIV with each 20 mmHg decrease in SBP equates to a slope of 0.5 of a linear regression of FIV with SBP. Therefore, the alternative hypothesis is that the slope of a linear relationship between SBP and FIV is numerically greater 0.5. Hence, a significant finding would be evidence that decreasing SBP increases FIV beyond a level which is considered safe, informing the lower limit for targeting SBP for testing in future trials (Figure 1).

Hypothesis 2: We consider 0.10 decrease in the UW-mRS scale from 0 (worst outcome) to 1 (best outcome) as clinically meaningful. A 0.10 decrease on the UW-mRS scale for every 20 mmHg decrease in SBP equates to a slope of -0.005 of a linear regression of UW-mRS with SBP. Therefore, the alternative hypothesis is that the slope of a linear relationship between SBP and the UW-mRS numerically less than -0.005, i.e. a larger negative slope. Hence, a significant finding would be evidence that decreasing SBP worsens UW-mRS, also informing the lower limit for targeting SBP for testing in future trials (Figure 1).

Figure 1. Statistical Hypotheses



9.2 SAMPLE SIZE DETERMINATION

Using the DEFUSE-3 trial data, we calculated the standard deviation of the difference in infarct volume from baseline to final for all patients. We conservatively assumed that collectively these values of the difference could represent the residuals of a linear regression between SBP as an independent variable and FIV in the worst-case scenario, where FIV demonstrates no association with SBP values. The standard deviation of residuals was 50 cc. Using the BEST-I data (our prospective, observational, multi-center study), we estimated the slope for the linear relationship of SBP and the UW-mRS. From this model, we calculated the standard deviation of residuals to be 0.37 and inflated this to 0.5 to be conservative.

With 101 subjects total, we will have 80% power using a one-sided test with the level of significance, alpha, of 0.05 to test both these hypotheses (Table 1). After accounting for a 15% loss to follow up for 90±14 -day outcome, our final sample size is 120 patients. FIV and UW-mRS will be treated as continuous variables with normal distribution.[25]

Table 1: Sample size calculation				
Outcome	Effect size[a]	Minimum Patients	Power[b]	Attrition
FIV Linear	⟩10 cc τ	101	80%	0%
UW-mRS Linear	⟩0.10 τ	101	80%	15%
Final Sample Size= 120 patients				
[a]per 20 mmHg decrease in post-EVT peak SBP target; [b]one-tailed α=0.05				

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants) will be used for primary analysis. The assigned intervention SBP groups will be used and evaluated, not the patients actual BP. Thus, the slopes of FIV and UW-mRS will be determined using the patient intervention SBP group assignment in regression models.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The BEST-II trial is designed to detect harm of the lower SBP targets; therefore, all statistical tests pertaining to the harm hypotheses will be one-tailed with an alpha to reject null hypothesis set at 0.05. Strength of evidence (e.g., confidence intervals around estimates) will be emphasized in addition to the level of significance in our reporting. Data will be screened for integrity prior to analysis. Statistical assumptions will be tested and appropriate data transformations and model adjustments will be made as needed. If it is determined that the proposed statistical plan cannot be conducted after reasonable adjustments, we will revert to alternative techniques (such as non-parametric approaches and non-linear modeling) to address the study aims.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

A mixed effects linear regression model will be generated to quantify the slopes of FIV and UW-mRS with low (<140 and <160 mmHg) and high (::180 mmHg) SBP targets. The assigned intervention SBP groups will be used and evaluated, not the patients actual BP. Thus, the slopes of FIV and UW-mRS will be determined using the patient intervention SBP group assignment in regression models. Rejection of the null hypothesis with a significant alpha would be evidence that decreasing SBP is unsafe. No corrections will be made for multiple hypothesis testing (please see below for justification). Covariables for the models for primary outcomes are defined *a priori*. We will adjust FIV for baseline ASPECT score and UW-mRS for baseline UW-mRS. We will also adjust analysis for both of the outcomes with the following variables as appropriate: age, baseline NIH stroke scale, and collateral circulation (assessed with modified Tan score), and site (where site will be treated as random effects). Regression diagnostics will be conducted on both models (for example, diagnostics for collinearity among predictor variables and overfitting). Age and baseline NIH stroke scale will be treated as continuous variables allowing for non-linearity using cubic splines with 3-5 knots that are not pre-positioned.

Justification for forgoing multiplicity correction: BEST-II is designed to detect harm of lowering SBP in successfully EVT-treated acute ischemic stroke patients. In this case, a type II error,

which is failing to detect harm, is more detrimental than type I error. We will not correct for multiplicity in order to maintain power at the expense of type I error. For example, with Bonferroni correction for multiplicity, a p-value less than 0.025 would be required for statistical significance. However, a p-value of 0.03 for primary safety endpoint (FIV), increases concern for harm of the intervention, despite being non-significant after multiplicity correction. By not correcting for multiplicity, BEST-II will more rigorously test for harm of the low SBP targets.

9.4.3 SAFETY ANALYSES

Interim analysis will be planned after a completed follow-up of 60 enrolled patients. We will terminate the study in favor of the alternative hypothesis (evidence of harm) for a p-value <0.025. Trial will not be terminated early for efficacy. No correction for alpha (i.e., alpha spending) will be made in the final analysis to maintain power.

AEs will be coded using the Medical Dictionary for Regulatory Activities. Each AE will be counted once only for a given participant. Severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. Start date, stop date, severity, relationship, expectedness, outcome, and duration will be reported for each AE. Adverse events leading to premature discontinuation from the study intervention and serious AEs will be presented either in a table or a listing.

9.4.4 PLANNED INTERIM ANALYSES

Interim analysis will be planned after a completed follow-up of 60 enrolled patients. Study will be terminated in favor of the alternative hypothesis of aim 1 (evidence of harm) for a p-value <0.025 for a slope of less than -0.5 for FIV or greater than 0.005 for UW-mRS. Trial will not be terminated early for efficacy. No correction for alpha (i.e., alpha spending) will be made in the final analysis to maintain power.

9.4.5 MISSING DATA

All attempts will be made to minimize missingness of the data. Any remaining missing data on covariates will be imputed using multiple imputations. Missingness of the primary outcomes is accounted for in the sample size calculations. However, to determine if missing data on primary outcomes is not at random, a sensitivity analysis will be conducted. We will fit a model to predict the missing FIV and UW-mRS (this model will not include the treatment variable) and this predicted outcome will be used to run an analysis similar to the primary analysis to determine the relationship of the treatment group with each outcome variable.

9.4.6 SUBGROUP ANALYSIS

Differential effect of SBP groups on each outcome will be determined according to age (as continuous variable), baseline ASPECT score, collateral grade, and reperfusion grade using interaction terms. In case of a significant interaction, a formal subgrouping analysis will be undertaken. An exploratory subgroup analysis according to ant-hypertensive use (yes or no) prior to admission will be undertaken.

9.4.7 DESCRIBING THE FIDELITY TO INTERVENTION

Fidelity to the assigned intervention will be represented both graphically and numerically. We will generate temporal profile plots for each patients observed SBP values (color coded according to assigned SBP groups) and by plotting average hourly SBP for each group against time. Further, we will report the average time spent below target for each group and the number of anti-hypertensives used (% of patients on 1,2,3, or >3 anti-hypertensive agents during the study period).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant if they are able to provide informed consent or their legally authorized representative as soon as the study team is able to contact them. The informed consent form is submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant or their surrogate healthcare decision maker will be asked to read and review the document. The investigator will explain the research study to the participant or their surrogate healthcare decision maker and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's or their surrogate

healthcare decision maker's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants or their surrogate healthcare decision makers will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants or their surrogate healthcare decision makers will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Participants and their surrogate healthcare decision makers will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document, either physical or electronic, will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All three arms of the BEST-II trial that the participants will be randomized to are considered standard of care with a documented equipoise. Any participant undergoing successful recanalization with mechanical thrombectomy could undergo blood pressure management similar to any of the arms in practice either at VUMC or other institution within the US. Additionally, our prior studies have shown that the blood pressure management must started immediately after recanalization to derive ideal benefit of each arm. On an average, after the first contact with the participant, all efforts are made to initiate the thrombectomy procedure and achieve recanalization as soon as possible.

1. If the participant is cognitively intact and is able to provide consent, the informed consent procedure will take place either in person or remotely using an electronic consent form. The study intervention will only be commenced once the participant has signed the informed consent form.
2. If the participant is cognitively impaired at presentation, the study personnel will reach their surrogate healthcare decision maker to obtain an informed consent. If the surrogate healthcare decision maker is remote from the study personnel obtaining consent, an electronic consent form can be sent via text message or email for their signature.
3. If the participant or their legally authorized representative decide to withdraw their participation in the study, the study intervention will be immediately stopped and patient will be provided standard of care as determined appropriate by the treating clinicians. The participant's data that is collected prior to the withdrawal will be used for research purposes and final analysis of the trial

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor

and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigator and her staff. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All data will be entered into electronic case report forms in a secured, password-protected database. The trial will utilize REDCap for data collection, transmission, and storage. REDCap is a secure, web-based application for building and managing online databases. VUMC maintains an institutionally-developed and updated software toolset and workflow methodology for electronic collection and management of research and clinical trial data. All study data will be entered via a password-protected REDCap database website unique for this study. REDCap servers are housed in an institutional, secured data center with regular backup, and all web-based information transmission is encrypted. REDCap was developed specifically to comply with all HIPAA-Security guidelines and is recommended by both the VUMC Privacy Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports >140 academic/non-profit consortium partners and 11,000 research end-users (*www.projectredcap.org*).

Only the minimum amount of PHI needed to conduct the study will be collected. All data collected will be generated during clinical care, and no additional data will be collected for research. At no time will we reveal subject identities in any manner, including research presentation, descriptions, or publications. As described above, all data will be entered into a secure, password-protected REDCap database. All patients will be assigned a unique patient identifier upon enrollment in the study. Patient identifiers will only be accessible to the PI and a select few research staff. Once the study results have been published, all study records will be stripped of any PHI in order to maximize patient and surrogate confidentiality.
The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Database will be locked and maintained a read-only mode once data are verified after the last patient completes the 90±14 -day follow up and until the time of study publication. At the time of publication, a de-identified version of the database will be generated. If a participant chooses to withdraw their authorization for study staff to access Protected Health Information (PHI), he or she may do so by notifying study staff in writing (the address will be provided on the consent form). In this case, actions will be taken to ensure that the data are properly destroyed and that the appropriate documentation is maintained, as is outlined in VUMC manual of standard operating procedures.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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615-936-3376
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10.1.6 SAFETY OVERSIGHT

A DSMB is appointed for study oversight and consists of physicians experienced in acute stroke, neuro-intensive care, and critical care medicine as well as a biostatistical expert. The DSMB will review the trial protocol and statistical analysis plan prior to enrollment of the first patient and suggest necessary changes. Following this, they will meet the earlier of hospital discharge of the 30th patient enrolled or 6 months from the date of the first participant enrollment via a teleconference meeting to review enrollment, protocol compliance, adverse events, and data quality. Following this first meeting, they will meet once every six months via teleconference.The DSMB will decide on their first meeting if members will be unblinded. In case the DSMB decides to remain blinded, one member will be unmasked. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Additionally, the DSMB will perform an interim analysis for safety events. In case of urgent issues, DSMB may convene a meeting at any time during the course of the trial. The DSMB will provide its input National Institutes of Health staff. Finally, DSMB will review final abstract and manuscript to ensure adequate study reporting.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. The PI and study coordinator will be responsible for resolution of any missing data or data anomalies.

Following department written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP).

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at VUMC under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. VUMC uses electronic medical record system for clinical documentation and data will be extracted from that and entered in to the REDCap electronic case report form. The PI will be responsible to ensure that the data recorded in the electronic case report form (eCRF) derived from source documents is consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap electronic case report form, a 21 CFR Part 11-compliant data capture system provided by the VUMC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The proposed research will primarily use data generated by the routine clinical care. All blood pressure data is exported daily from the electronic health record to the Enterprise Data Warehouse at VUMC, which will be electronically extracted. Quality of this data extraction has been previously validated with two-physician manual chart review.[31,40,41] This data will also be used for compliance monitoring. Data will also be automatically pulled from Vanderbilt University Medical Center (VUMC)’s electronic health record system integrated with this project-specific REDcap database using the Dynamic Data Pull on Fast Healthcare Interoperability Resources (DDP on FHIR) feature.

Electronic data elements to be collected: [1] Baseline Characteristics: age; gender; ethnicity; admission, ICU, and discharge vital signs (SBP, diastolic BP, mean arterial BP, pulse); baseline comorbidities (hypertension, diabetes, hyperlipidemia, stroke, atrial fibrillation, smoking); home medications (antiplatelets, anticoagulants, antihypertensives); baseline NIH stroke scale; laboratory values (blood serum glucose, international normalized ratio, platelets) [2] Medications: intravenous tissue plasminogen activator administration, in-hospital Medications: total amount of nicardipine and labetalol administered; use of any other anti-hypertensive agents; vasopressor requirement [3] Clinical Outcome Measures: 24-hr NIH stroke scale; in-hospital death; 90±14 -day modified Rankin score.

Additionally, trained study personnel will *manually extract* the following elements collected as routine clinical care: [1] Time of events such as patient's last known well, arrival to emergency department, groin puncture to initiate EVT, final recanalization, and intervention initiation; [2] all adverse events and protocol violations; [3] final mTICI score on angiogram.

Automated imaging data to be collected: All LVO stroke patients at VUMC undergo baseline CT perfusion studies with automatic, computationally generated calculations of core and penumbra volumes and hypoperfusion intensity ratios (to assess collateral circulation) using the iSchemaView RAPID software. These values will be extracted. Additionally, core and penumbra volumes on 36±12-hr MRI perfusion sequence will also be calculated using the iSchemaView RAPID software.

Manual imaging data to be collected: [1] Alberta Stroke Program Early CT score (ASPECTs) on the baseline brain CT [2] location of vessel occlusion on baseline CT angiogram [3] presence and characteristic of any hemorrhage on 36±12-hr MRI brain [4] 36±12-hr MRI or CT scan brain infarct volume by a blinded trained person and confirmed by an expert neuroradiologist.

Validation: The study coordinator will manually collect all BP values within 24-hr post-treatment initiation and a 90±14 -day modified Rankin score on 100% of the patients, in addition to all variables of data on randomly selected (i.e. 33% [n=40]) patients for validation.

10.1.9.2 STUDY RECORDS RETENTION

Study database will be locked and maintained a read-only mode once data are verified after the last patient completes the 90±14 -day follow up and until the time of study publication. At the time of publication, a de-identified version of the database will be generated. If a participant chooses to withdraw their authorization for study staff to access Protected Health Information (PHI), he or she may do so by notifying study staff in writing (the address will be provided on the consent form). In this case, actions will be taken to ensure that the data are properly destroyed and that the appropriate documentation is maintained, as is outlined in VUMC manual of standard operating procedures.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

PI will be responsible to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations will be addressed in study source documents, reported to NINDS Program Official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 years after the completion of the primary endpoint by contacting Eva Mistry, MBBS at Vanderbilt University Medical Center (eva.a.mistry@vumc.org).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS will ensure that study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	11/13/2019	It is clarified that the Final infarct volume will be calculated on 36±12 hours and modified Rankin Score will be obtained at 90±14 days.	The changes are made for consistency throughout the protocol and allow for the number of days that it might take to reach the patient at 90 days.
1.0	11/13/2019	Time of randomization is changed to after achievement of successful recanalization.	The changes are requested in order to allow the separation of clinical and research consenting process to allow adequate time for research consenting. Additionally, the changes requested will simplify the trial logistics and will provide a more homogenous population of interest (only successfully treated patients) for the primary intention to treat analysis. In the original protocol, the intention was to only follow patients with unsuccessful recanalization.
1.0	11/13/2019	Study intervention will start after randomization (which will occur after successful recanalization is achieved per the change requested above)	The change requested reflects the slight change in the trial workflow to allow randomization to occur after successful recanalization and to let the intervention begin promptly after randomization.
1.0	11/13/2019	Method of randomization is changed to stratified permuted block randomization from simple randomization.	The requested change will allow a homogenous distribution of 40 patients in each arm. Simple randomization may have led to unequal distribution of number of patients in each arm.
1.0	11/13/2019	Spelling and language changes are made	Changes are requested for clarity
1.0	11/13/2019	It is clarified that the PI, and not the DSMB, will be responsible for determining whether an adverse event is expected or unexpected.	The changes requested will allow for faster reporting of the AEs to the IRB, as the DSMB meetings will be

			schedule on a biannual basis.
2.0	10/20/20	Perfusion criteria requiring baseline CT or MR perfusion is deleted	This inclusion criteria was initially required to account for the differences in the baseline infarct volumes of patients included in the trial in the final analysis. Recent data has suggested that the baseline non-contrast CT brain (acquired as routine care in all stroke patients) can reliably measure this infarct burden and advances scanning techniques such as perfusion scans are no better at this estimation. Thus to simplify trial enrollment criteria, the requirement of a baseline CT or MR perfusion scan is no longer required.
2.0	10/20/20	Follow-up perfusion outcome removed	This outcome is removed as it is not routinely obtained as clinical care.

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