Stryker Neurovascular

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DAWN™ Trial Investigator Agreement

I have read this Investigational Plan and agree to adhere to the requirements of this current version of the protocol.

I agree to personally conduct or supervise the research, and ensure all participating investigators and research staff are appropriately informed and trained prior to participating in any study related activities.

I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50, ICH E6 and institutional review board/Ethics Committee (IRB/EC) review and approval in 21 CFR Part 56 are met. I will ensure that the IRB/EC complies with the requirements of ICH E6 and 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the investigation. I agree to promptly report to the IRB/EC and to the Sponsor all changes in the research activity and all unanticipated problems involving risks to human subjects or others. I will not make any changes in research without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in ICH E6 and 21 CFR Part 812, and/or the laws and regulatory requirements of the country in which the site is located.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 812.145 and ICH E6.

I agree to comply with all state and federal laws and regulations governing financial disclosure and to supply updated disclosure information, as it becomes known to me, during the course of the Trial and for one year following completion of the Trial, unless otherwise required by law or regulation.

I have not been restricted from participating in clinical research, nor is any action pending that could result in such restriction. If this occurs I shall provide immediate notification to the Sponsor.

I have NOT been involved in an investigation or other research that was terminated:

☐ True ☐ False

If False, please provide an explanation (including the circumstances that led to the termination):

_____

_____

Investigator Name (print) Signature dd-mmm-yyyy

_____

Co-Investigator Name (print) ☐N/A Signature dd-mmm-yyyy

Protocol Synopsis

DAWN™ Trial

DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention

Study Objective	
Primary Objective	To evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well.
Secondary Objective(s)	To provide evidence that endovascular reperfusion with Trevo is associated with a significant reduction in median infarct size compared to the control group at 24 (-6/+24) hours post randomization.
Test Device	Trevo® ProVue™ and Trevo® XP ProVue™ Retrievers
Study Design	
Study Design	Prospective, randomized, multi-center, Phase II/III (feasibility/pivotal), adaptive, population enrichment, blinded endpoint, controlled trial.
Planned Number of Subjects	A maximum of 500 subjects is planned to be enrolled; 250 in the Treatment arm and 250 in the Control arm. The minimum sample size is 150 subjects.
Planned Number of Sites / Countries	Worldwide (up to 50 sites). No more than 20 sites will be outside of the U.S.
Primary Endpoint	90-day disability assessed by the modified Rankin scale (mRS)
Secondary Endpoints	1. Proportion of subjects with a good functional outcome at 90 days, defined as mRS 0-2 2. Proportion of subjects with "early response" at Day 5-7/Discharge (whichever is earlier), defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1 3. Difference in all cause mortality rates between the two groups. 4. Difference in median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if contraindicated for MR) 5. Difference in revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA. 6. Treatment Arm Only: Analysis of vessel reperfusion rates (percentages) post device and post procedure, by angiography core lab measurement of modified TICI ≥ 2b

<table>
<tr><td>Primary Safety Outcome</td><td>Both Arms:
1. Incidence of stroke-related mortality at 90 days</td></tr>
<tr><td>Secondary Safety Outcomes</td><td>Both Arms:
1. Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero)
2. Incidence of neurological deterioration from baseline NIHSS score through Day 5-7/discharge (whichever is earlier) post randomization (time zero). Neurological deterioration is defined as ≥ 4 point increase in the NIHSS score from the baseline score.
Treatment Arm:
3. Incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post randomization (time zero) as adjudicated by the clinical events committee, and defined as:
a. vascular perforation
b. intramural arterial dissection
c. embolization to a new territory
d. access site complication requiring surgical repair or blood transfusion
e. intra-procedural mortality
f. device failure (in vivo breakage)
g. any other complications adjudicated by the CEC to be related to the procedure</td></tr>
<tr><td>Efficacy Parameter</td><td>Modified Rankin Scale score at 90 days:
0 - No symptoms at all
1 - No significant disability despite symptoms; able to carry out all usual duties and activities
2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3 - Moderate disability; requiring some help, but able to walk without assistance
4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 - Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6 - Dead
Note: For purposes of primary efficacy weighted mRS analysis each mRS category will be assigned a numerical value representing its clinical utility, as follows:
<table><tr><td>mRS</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr><tr><td>Weight</td><td>10</td><td>9.1</td><td>7.6</td><td>6.5</td><td>3.3</td><td>0</td><td>0</td></tr></table></td></tr>
<tr><td>Randomization</td><td>Subjects will be randomized 1:1 to Trevo thrombectomy plus medical management or medical management alone.
Stratification will occur by: Clinical Imaging Mismatch (CIM) subgroup (see Imaging Inclusion Criteria), Time Last Seen Well (TLSW) ≥ 6 to ≤ 12 hours vs. >12 to ≤ 24 hours, and Baseline Occlusion Location (ICA vs. M1).
After randomization, no crossover is permitted.
Enrollment in this study is defined as the moment when the randomization process is completed and the subject is assigned to a study arm.</td></tr>
</table>

Study Duration	• Enrollment: approximately 36 months • Subject participation: 90 days (± 14) • Total Study Duration: approximately 39 months (+/- 9 months)
Follow-Up Schedule	All follow up time points are relative to time of randomization (time zero) with baseline data considered as data generated from time of index stroke admission and prior to randomization. 1. 24 (-6/+24) hours: MRI/MRA or CT/CTA (if MR is contra-indicated) and NIHSS assessment. Final infarct volume will be measured by MRI T2/Flair or CT (if MR is contraindicated). 2. Day 5-7 (if subject remains in hospital) or discharge, whichever is earlier: NIHSS and blinded mRS (Optional repeat MRI T2/Flair or CT, if MR is contraindicated, may be performed to assess infarct volume) 3. Day 30 (± 14): NIHSS and blinded mRS 4. Day 90 (± 14): NIHSS and blinded mRS
General Inclusion Criteria	1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups: a. Subject has failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration) b. Subject is contraindicated for IV t-PA administration 2. Age ≥18 3. Baseline NIHSS ≥10 (assessed within one hour of measuring core infarct volume) 4. Subject can be randomized between 6 to 24 hours after time last known well 5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1) 6. Anticipated life expectancy of at least 6 months 7. Subject willing/able to return for protocol required follow up visits 8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form* * If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient utilizing emergency informed consent procedures if neither the patient nor the representative or person of trust is available to sign the informed consent form. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research. (Not applicable to U.S. Sites.)
General Inclusion Criteria (additional information)	1. Subjects receiving heparin or low molecular weight (LMW) heparin e.g. Fragmin® (Dalteparin Sodium) or an intravenous direct thrombin inhibitor such as Angiomax® (Bivalirudin), or Argatroban within the last 24 hours from screening are eligible for participation if their coagulation profile remains acceptable. 2. Subjects on factor Xa inhibitors (e.g. apixaban) or direct thrombin inhibitors are eligible for participation
Imaging Inclusion Criteria	1. < 1/3 MCA territory involved, as evidenced by CT or MRI 2. Occlusion of the intracranial ICA and/or MCA-M1, as evidenced by MRA or CTA 3. Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps: a. 0-<21 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old) b. 0-<31 cc core infarct and NIHSS ≥ 10 (and age < 80 years old) c. 31 cc to <51 cc core infarct and NIHSS ≥ 20 (and age < 80 years old)

General Exclusion Criteria	1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history 2. Rapid improvement in neurological status to an NIHSS <10 or evidence of vessel recanalization prior to randomization 3. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. dementia with prescribed anti-cholinesterase inhibitor (e.g. Aricept) 4. Seizures at stroke onset if it makes the diagnosis of stroke doubtful and precludes obtaining an accurate baseline NIHSS assessment 5. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol) 6. Baseline hemoglobin counts of <7 mmol/L (11.28 g/dL) 7. Baseline platelet count < 50,000/uL 8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L 9. Renal failure as defined by a serum creatinine >3.0 mg/dL (264 µmol/L) NOTE: subjects on renal dialysis may be treated regardless of serum creatinine levels 10. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal. NOTE: Patients on factor Xa inhibitor within 24-48 hours must have PTT within 3 times normal. 11. Any active or recent hemorrhage within the past 30 days 12. History of severe allergy (more than rash) to contrast medium 13. Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg) NOTE: If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled 14. Female who is pregnant or lactating at time of admission 15. Current participation in another investigational drug or device study 16. Presumed septic embolus, or suspicion of bacterial endocarditis 17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	1. The "correction" of baseline glucose or coagulation laboratory values to meet inclusion criteria will not be allowed. 2. Subjects who have taken Clopidogrel, aspirin, or both within the last 24 hours from screening for the trial should not be excluded if their coagulation profile remains acceptable. 3. Subjects with a questionable seizure at onset of stroke should not be excluded if CTA/MRA confirms the presence of intracranial ICA and/or M1 occlusion, and accurate NIHSS can be obtained.
Imaging Exclusion Criteria	1. Evidence of intracranial hemorrhage on CT/MRI 2. CTA or MRA evidence of flow limiting carotid dissection, high-grade stenosis, or complete cervical carotid occlusion requiring stenting at the time of the index procedure (i.e., mechanical thrombectomy). 3. Excessive tortuosity of cervical vessels on CTA/MRA that would likely preclude device delivery/deployment 4. Suspected cerebral vasculitis based on medical history and CTA/MRA 5. Suspected aortic dissection based on medical history and CTA/MRA 6. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device

	7. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior circulation/vertebrobasilar system) as confirmed on CTA/MRA, or clinical evidence of bilateral strokes or strokes in multiple territories 8. Significant mass effect with midline shift as confirmed on CT/MRI 9. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI
Concomitant Medication Therapies	Treatment Arm: 1. Use of IV or IA lytics, or IA antiplatelets is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed. 2. Systemic anticoagulation with heparin may be used during the procedure, but should not exceed a total of 2,000 units of heparin bolus followed by a 500 units/hour drip for the duration of the procedure. 3. Prudent use of anti-vasospasm agents is permitted during the procedure. Medical Management Arm: 4. IV heparin is prohibited until after the 24 (-6/+24) hour neuro-imaging has been performed to determine the presence/absence of intracranial hemorrhage. 5. The administration of medications is at the treating physician's discretion according to local standards of care, but may NOT include any intra-arterial therapies. Both Arms: 6. Newly administered Aspirin (IV or oral) and/or Clopidogrel are the only anti-platelets allowed within the first 24 hours post randomization, until after the 24 (-6/+24) hour neuro-imaging has been performed to determine the presence/absence of intracranial hemorrhage. 7. Subjects previously treated with antiplatelet agents or combination antiplatelet therapy (e.g. for a previously implanted drug eluting stent), may continue this if in the investigator's opinion the benefits of continued therapy outweigh the risks of potential neurological deterioration related to hemorrhage. 8. Subcutaneous Low Molecular Weight (LMW) heparin is allowed for Deep Vein Thrombosis (DVT) prophylaxis per the center's standard of care.
Multiple Interventions	Once randomized, subjects in either arm may not be treated with any additional planned endovascular therapy or endarterectomy until after the 24 (-6/+24) hour post randomization assessments have been completed.
Statistical Methods	
Primary Statistical Null Hypothesis	The null hypothesis is that there is no difference in the proportion of subjects functionally independent (mRS 0-2) at 90 days in the Trevo Thrombectomy plus Medical Management group compared to Medical Management alone nor in the average of the weighted mRS categories at 90 days in the Trevo Thrombectomy plus Medical Management group compared to Medical Management alone.
Statistical Test Method	The alternative hypothesis is that the proportion of subjects functionally independent (mRS 0-2) and the average of the weighted mRS categories at 90 days in the Trevo Thrombectomy plus Medical Management group is superior to Medical Management alone. The final analysis is a Bayesian analysis of the 90-day mRS scores, and declares success if there is sufficiently large posterior probability that the overall treatment effect is positive. The threshold for success if no enrichments are made is 0.986, and this threshold increases as the enrichment becomes earlier and more aggressive. The adjusted thresholds are to control type I error. Enrichment decisions and early stopping rules are based on Bayesian predictive probabilities outlined in the Adaptive Design Plan in **Appendix F**.

Sample Size Parameters	The sample size for the trial is assessed through simulation, which considered effect sizes ranging from zero to a 1.5 increase on the weighted mRS scale. For one-sided Type I error probability of 2.5%, the design has 86% power for a 1 unit increase in weighted mRS.

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1 Introduction and Rationale

1.1 Incidence and Burden of Stroke

Stroke represents the fourth leading cause of death in industrialized nations, after heart disease, cancer, and chronic lower respiratory disease. Each year approximately 795,000 people experience a new or recurrent stroke (ischemic or hemorrhagic) in the U.S. Also, in 2009, stroke caused approximately 1 of every 18 deaths in the United States. On average, every 40 seconds, someone in the United States has a stroke and dies of one approximately every four (4) minutes. [1-2]

Proximal intracranial arterial occlusions are common, cause the most disabling types of ischemic strokes, and are predictive of poor neurological outcomes at hospital discharge. [3] Stroke survivors constitute the majority of disabled people nationally in the United States. Approximately one-quarter of the patients suffering a stroke die within one year after the initial event. Stroke brings a dramatic financial and personal burden to society. Direct medical costs related to stroke in the United States is an estimated $28.3 billion per year. Stroke is a leading cause of serious long-term disability. [4]

1.2 Current Treatment Options

Intravenous (IV) tPA (alteplase) remains the only approved therapy for acute ischemic stroke (AIS). However, IV tPA has many limitations, including a short therapeutic window, with administration being restricted in the United States to 3 hours post known symptom onset, and in other parts of the world to 4.5 hours post known symptom onset, and a strong time-dependency. [5-8] The efficacy of IV tPA is limited by the large thrombus burden that occurs in the setting of acute ischemic strokes caused by proximal intra-cranial arterial occlusions. [9] [10]

In the 0-8 hours post symptom onset, endovascular revascularization by mechanical embolectomy has been shown to be safe and effective in numerous studies, including the MERCI and Multi MERCI trials [11-12], the Penumbra Pivotal trial [13], and the SWIFT and TREVO 2 trials [14-15]. Clinical outcomes in ischemic stroke have been shown to be strongly linked to revascularization. [16-18] Thus, in cases where patients are ineligible for IV tPA or where IV tPA fails to result in a clinical improvement, endovascular treatment with mechanical thrombectomy devices is a viable treatment option. Mechanical endovascular therapy has been linked to higher recanalization rates as compared to IV tPA, and is considered standard of care in many institutions within the 0-8 hour time window. [19-21]

1.3 Unmet Need in Acute Ischemic Stroke

Acute ischemic stroke due to large vessel occlusion (LVO) is a potentially devastating event, with a poor prognosis in the absence of timely revascularization. The sub-population of interest in this study is subjects with intracranial ICA or MCA-M1 vessel occlusions. Evidence from

prior and ongoing studies suggests that patients with a blockage in these vessels, when managed medically, do worse compared to those who are treated with pharmacologic or mechanical reperfusion therapies.

In a single center study conducted in Badalona, Spain of consecutively screened patients within 6-24 hours of symptom onset or time they were last seen well, the subset of medically managed patients with confirmed intracranial ICA or MCA-M1 occlusions, 17.5% of patients experienced a good clinical outcome, defined as a modified Rankin Score (mRS) of 0, 1 or 2. [22]

In the multi-center STOPSTROKE study, good outcomes in a clearly defined subset of medically managed patients with CTA confirmed intracranial ICA or MCA-M1 occlusion was 18.4%. Although treated patients in this study presumably had more favorable imaging at baseline and therefore their natural history may be more favorable than untreated patients, the evidence is suggestive of worse outcomes in untreated patients. [23]

The ongoing Penumbra FIRST study includes subjects presenting within 0-8 hours from symptom onset with documented ICA or M1 occlusions who would normally be candidates for endovascular thrombectomy, but for whom the procedure is unavailable. The interim outcomes data for the first 63 subjects enrolled demonstrate a good outcome rate of 20.4%. [24]

The seminal PROACT II trial control arm, which included subjects with MCA-M1 and M2 occlusions, is often referenced as a comparator for results of treatment with pharmacological or mechanical revascularization therapies. In PROACT II, the control arm subjects were treated with intra-arterial heparin within 0-6 hours of symptom onset. This group of subjects experienced good clinical outcomes in 25% of the cases. [25-26] However, in the more proximal MCA-M1 occlusion subset of the control arm (n=37) good outcomes were only 22%. [27]

Together, these data support an overall grim prognosis for medically managed intracranial ICA or MCA-M1 occlusions, with low rates of good outcomes ranging from 17.5-25%.

In contrast to patients who are medically managed, those with similar clinical presentation who are revascularized experience higher rates of good clinical outcomes. In the SWIFT and TREVO 2 trials, Stentrievers™ were used to restore blood flow to the neurovasculature in subjects with intracranial large vessel occlusions. Subjects treated within 0-8 hours of symptom onset experienced good clinical outcomes in 37% and 40% of cases respectively. [14-15] In a retrospective analysis of stroke patients, who were selected by CT Perfusion or MRI for endovascular treatment, regardless of time from symptom onset or time last seen well, Nogueira et al reported good outcomes of 40% within the subset of patients with confirmed intracranial ICA or MCA-M1 occlusions. [28]

The current guidelines for treatment, including the use of thrombolysis and/or thrombectomy are based on time last seen well (TLSW). [29] Yet, the majority of patients presenting with AIS symptoms are beyond 8 hours from symptom onset or of unknown onset. [30] It is estimated that in between 14-28% of AIS patients, the onset of stroke symptoms is un-witnessed or occurs during sleep. [31-36] It has also been demonstrated that as many as 71.4% of the patients with proximal intra-cranial arterial occlusion may have a significant MRI (DWI/PWI) mismatch as far as 9 to 24 hours post stroke onset. [37]

There is limited data in the literature on the relative risks versus benefits of performing mechanical thrombectomy in patients within 6-24 hours from symptom onset or time last seen well. The current AHA/ASA guidelines recommend standard medical management only (supportive care) for these patients. [29] The AIS stroke population is heterogeneous by nature and though some patients may do better than others, in general the more proximal the occlusion and the later the patient arrives, the worse the anticipated outcome.

1.4 Purpose of Study

The intent of this study is to support the use of the Trevo Retriever beyond the currently labeled 8 hour indicated time limit in wake up, unclear onset, and late presenting ischemic stroke subjects, who currently have no other option besides medical management of their symptoms.

Patients with wake-up strokes, strokes with unclear onset time, and witnessed late presenting strokes may potentially benefit from intra-arterial reperfusion therapy. [28, 35, 38-44] However, an important indicator of whether subjects will benefit or not during this later time window is the confirmation of a large vessel occlusion (LVO), and assessment of the core infarct volume relative to the volume of salvageable penumbra. [45-47] Therefore, standardized imaging selection of subjects is required for inclusion into the study.

This trial has been designed with subject safety in mind, as a seamless Phase II (feasibility) / Phase III (pivotal) adaptive design, in order to address the concerns around potential unknown harms to enrolled subjects. This study will help to answer the question of whether carefully selecting subjects by using Clinical Imaging Mismatch will allow acute ischemic stroke patients who present at or beyond 6 hours from Time Last Seen Well (TLSW) to be considered for intra-arterial intervention. If Trevo thrombectomy plus medical management leads to better clinical outcomes over medical management alone, more patients in the future could receive endovascular treatment (either in addition to or in lieu of IV tPA).

2 Study Device

2.1 Study Device Description

The study devices include the Trevo ProVue and XP ProVue Retrievers manufactured by Concentric Medical, a business unit of Stryker Neurovascular. Compared to the cleared devices, the study devices differ only by their modified Indications for Use. Key dimensions

of study devices are summarized in Table 1. Various device sizes may be added to the study upon receiving regulatory approval including an IDE supplement. Only devices labeled for investigational use are to be used.

Table 1. Key Dimensions of Trevo Family Retrievers

Trevo Retriever Size	Investigational Model #	Overall Length	Clot Capture Area (Active Shaped Section Length)	Total Shaped Section Length	Shaped Section Diameter
Trevo ProVue Retriever					
4x20mm	90191, 90291	180cm	20mm	37mm	4mm
Trevo XP ProVue Retrievers					
3x20mm	90192, 90292	190cm	20mm	36mm	3mm
4x20mm	90193, 90293	180cm	20mm	32mm	4mm
6x25mm	90194, 90294	180cm	25mm	40mm	6mm
4x30mm	90195, 90295	180cm	30mm	44mm	4mm

The cleared Indications for Use for the Trevo ProVue and XP ProVue Retrievers is as follows:

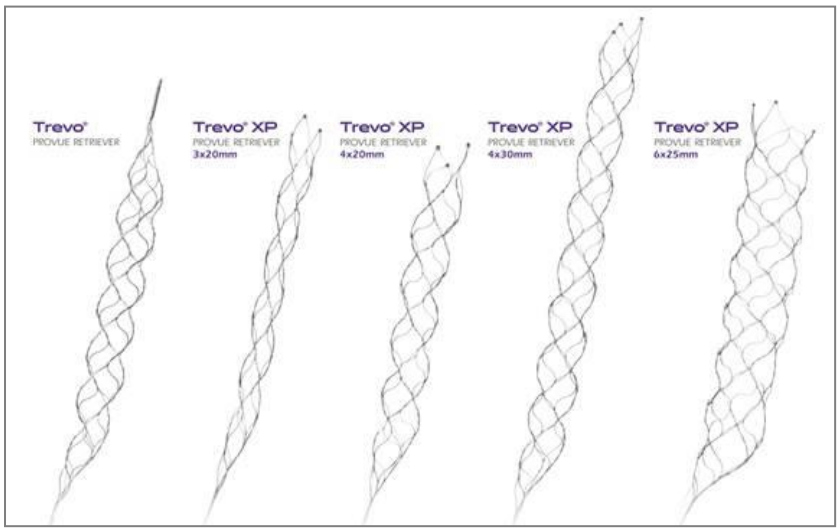
The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.

The proposed Indications for Use for the Trevo ProVue and XP ProVue Retrievers utilized in the DAWN™ Trial are as follows:

The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 24 hours of symptom onset. The Trevo Retriever is also intended to improve neurological outcomes in patients experiencing ischemic stroke between 6 – 24 hours of symptom onset."

Apart from the modified proposed Indications for Use, the study devices are identical to the cleared devices and consist of a flexible, tapered core wire with a shaped Nitinol section at the distal end for clot capture. As shown in **Figure 1,** The Trevo ProVue Retriever has a radiopaque platinum coil at the distal end of the shaped section while the Trevo XP ProVue Retrievers have platinum markers at their distal ends. All Trevo Retrievers contain platinum wires woven throughout the shaped section with radiopaque solder at the proximal end to facilitate fluoroscopic visualization. The devices have a proximal shaft marker to indicate proximity of the Retriever tip relative to the microcatheter tip and a hydrophilic coating to reduce friction. A torque device and an insertion tool are provided with the Trevo Retrievers. Retriever dimensions are indicated on the product labels.

Figure 1. Examples of Trevo Retrievers



During the study procedure, the operator may choose which Trevo Retriever to use, depending upon anatomical considerations and personal preference. The Trevo Retriever is delivered to the thrombus using a microcatheter. The microcatheter is then retracted to deploy the shaped section of the Retriever. The Retriever and microcatheter are pulled back to dislodge the thrombus. The Retriever, the thrombus, and the microcatheter are then removed from the body.

The Trevo Retriever has been designed and tested to perform multiple retrieval attempts in a single vessel. Per the IFU no more than six (6) passes within the same vessel should be made using any combination of Trevo Retrievers. Each device can be used for up to three retrieval attempts.

After each deployment of the Trevo Retriever it should be thoroughly inspected before reloading.

Refer to the Instructions for Use (IFU) for detailed instructions on how to prepare and use the Trevo Retriever. The devices should not be re-sterilized and reused.

There are no specific contraindications for the use of the Trevo Retrievers apart from the inclusion and exclusion criteria of this protocol. Refer to the IFU for a listing of warnings and precautions.

2.2 Study Device Labeling

The Trevo Retriever study devices are labeled consistent with CFR 812.5 (a), and shall bear the following information:

- the name and place of business of the manufacturer

- packer, or distributor (in accordance with 801.1)
- the quantity of contents, if appropriate
- the following statement: " CAUTION: Investigational device. Limited by United States law to investigational use. Exclusively for Clinical Investigations. Investigational Device. To be Used by Qualified Investigators Only." (Label will be applied to the outside of the Trevo Retriever pouch and to the outside of the carton containing the Trevo Retriever)

In addition, the study device labels contain device dimensions, Lot Number, and expiration (use before) date.

The DAWN IDE Investigational Instructions for Use (IFU) shall be packaged with the study device, and describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. A sample IFU is attached as **Appendix E**.

The study device may be provided to sites as single units, or as components within convenience packs, which contain a non-investigational microcatheter that is compatible with the Trevo Retriever.

3 Study Objective

3.1 Primary Objective

To evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well.

3.2 Secondary Objectives

To provide evidence that endovascular reperfusion with Trevo is associated with a significant reduction in median infarct size compared to the control group at 24 (-6/+24) hours post randomization.

4 Study Endpoints and Safety Outcomes

The following clinical endpoints and safety outcomes will be evaluated in all subjects who are randomized whether or not the randomized study treatment is successfully administered, also called the Intent to Treat (ITT) group of subjects.

4.1 Primary Endpoint

The primary endpoint is the 90-day clinical outcomes assessed by the modified Rankin scale (mRS).

The primary endpoint analysis will consist of a comparison of the difference in proportion of functional independence (mRS 0-2) at 90 days post randomization between the active and control arm (dichotomous analysis) as well as the difference between the average weighted modified Rankin Scale (mRS) score at 90 days post randomization between the active and control groups (weighted mRS analysis). For the latter, each mRS category is assigned a numerical value representing its clinical utility, based on the work by Rivero-Arias, et al and Hong and Saver, as described in the Adaptive Design Plan in **Appendix F**. [48-49]

4.2 Secondary Endpoints

Both Arms:

1. Comparison of the proportion of subjects with a good functional outcome at 90 days, defined as mRS 0-2, between the active and control groups.
2. Comparison of the proportion of subjects with "early response" at Day 5-7/Discharge (whichever is earlier), defined as a NIHSS drop of ≥10 from baseline or NIHSS score 0 or 1, between the active and control groups.
3. Difference in all cause mortality rates between the two groups.
4. Comparison of the median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if MR is contraindicated), between the active and control groups.
5. Difference in revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA.

Treatment Arm only:

6. Analysis of vessel reperfusion rates (percentages) post device and post procedure, by angiography core lab measurement of modified TICI ≥ 2b.

4.3 Primary Safety Outcome

Both Arms:

1. Incidence of stroke-related mortality at 90 days

4.4 Secondary Safety Outcomes

Both Arms:

1. Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero)
2. Incidence of neurological deterioration from baseline NIHSS score through Day 5-7/discharge (whichever is earlier) post randomization (time zero). Neurological deterioration is defined as ≥ 4 point increase in the NIHSS score from the baseline score.

Treatment Arm only:

3. Incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post randomization (time zero), as adjudicated by the clinical events committee (CEC), and defined as:

   - vascular perforation
   - intramural arterial dissection
   - embolization to new territory
   - access site complication requiring surgical repair or blood transfusion
   - intra-procedural mortality
   - device failure (*in vivo* breakage)
   - any other complications adjudicated by the CEC to be related to the procedure

5 Study Design

5.1 Overview

The DAWN protocol is a prospective, randomized, multi-center, Phase II/III (feasibility/pivotal), adaptive, controlled trial, designed to demonstrate that mechanical thrombectomy using the Trevo Retriever with medical management is superior to medical management alone in improving clinical outcomes at 90 days in appropriately selected wake up and late presenting acute ischemic stroke subjects. **Figure 2** shows the flow of subjects through the screening, randomization assignment and follow up phases of the study.

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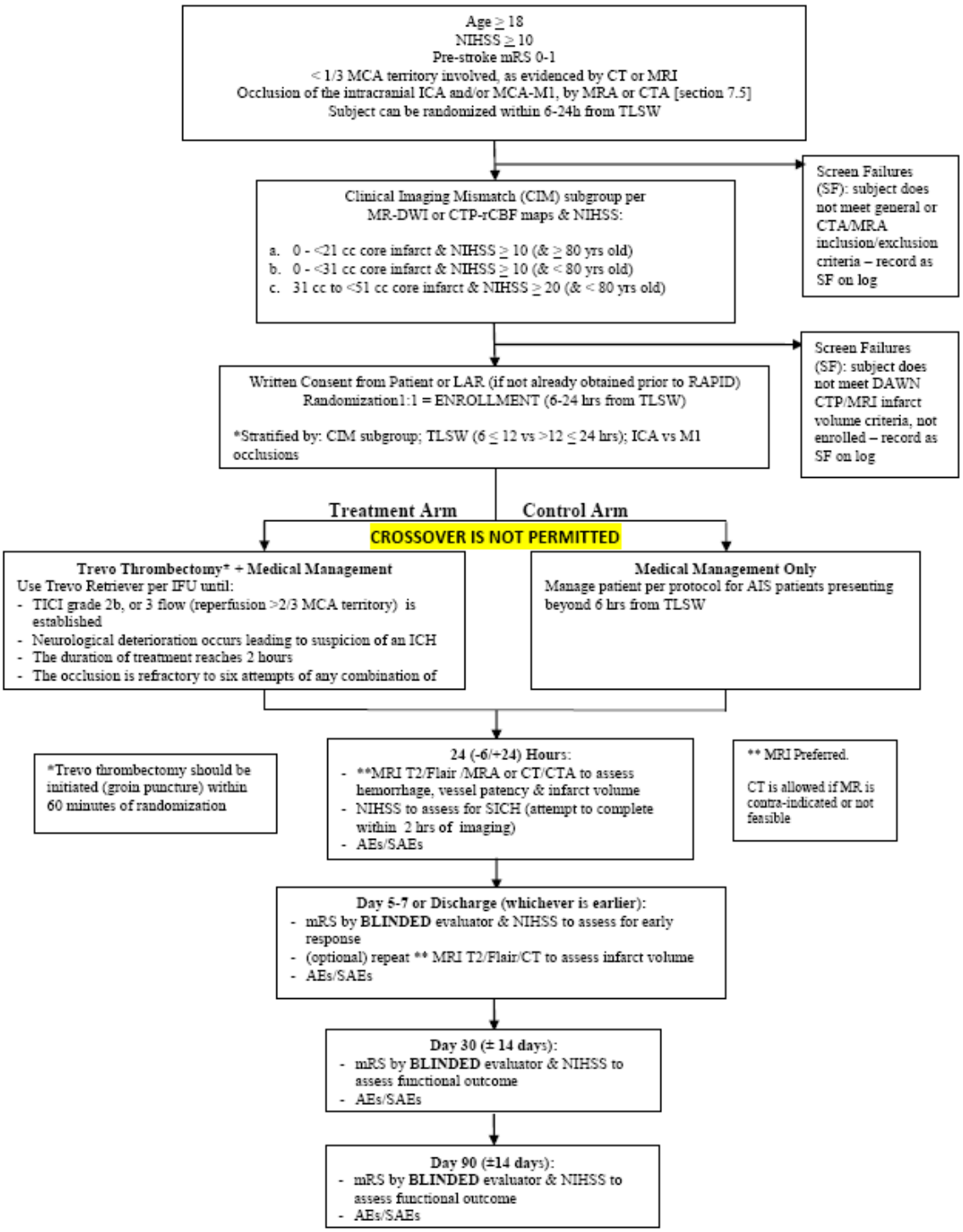
Figure 2. DAWN™ Trial Flow Chart



5.2 Justification for the Study Design

Previous studies of mechanical embolectomy devices, conducted in order to gain regulatory approval, were either single arm studies comparing revascularization rates against the observed control rate in PROACT II (18%), or more recently, studies comparing newer generations of thrombectomy devices against older ones. Since none of these studies randomized against a *concurrent* control arm, it is not known if the rates of good outcomes, mortality and symptomatic ICH are better, the same, or worse with mechanical endovascular intervention than without it. [11-15]

Although a correlation has been demonstrated between good clinical outcomes and endovascular reperfusion in numerous independent studies, [16-18] and revascularization rates have increased steadily with the advent of Stentrievers™ such as the Trevo and Solitaire devices, the corresponding rates of good clinical outcomes have not increased substantially. Several non-controlled studies using a variety of endovascular procedures have reported rates of successful recanalization ranging from 46% to 90%, and good outcomes at 90 days, ranging from 25% to 55%. [13-15, 50-57]

The neutral results of the IMS III, MR RESCUE and SYNTHESIS Expansion trials bring into question the relative benefits of mechanical thrombectomy as adjunctive therapy to IV tPA in the earlier time windows. [58-60] These trials have been critiqued for potential flaws in their design and execution, including the potential of subject selection bias due to lack of equipoise to randomize in the earlier time window; a lack of confirmation of a large vessel occlusion (LVO) on initial presentation in some subjects; the use of predominantly older technology devices; and the use of combined intra-arterial approaches, making it difficult to know what device or therapy resulted in what effect. [61-62]

There is growing evidence to support selecting patients for reperfusion therapy by using neuro-imaging to evaluate brain tissue status as opposed to using time from stroke onset. The results of three non-randomized studies which looked at outcomes in patients selected for thrombolysis within and beyond 3 hours using MR imaging compared with standard CT-based selection criteria suggested that the MRI-based approach might be advantageous. [39-41] Following the implementation at Massachusetts General Hospital of the MRI based selection for patients with acute large vessel occlusion (LVO) for intra-arterial (IA) therapy, a significant one-category improvement in the mRS was demonstrated, presumably by targeting patients more likely to benefit and removing patients unlikely to benefit, or even be harmed, by IA therapy. [63]

Three distinct tissue states in the ischemic brain are defined below, according to their potential to return to normal biological functioning: (1) brain that is non-functional and irreversibly damaged (infarct core); (2) potentially salvageable hypo-perfused brain that is functionally impaired but structurally intact and is destined to undergo infarction in the absence of reperfusion (salvageable penumbra); and (3) hypo-perfused brain that is both functionally and

structurally intact and will not undergo infarction even in the absence of reperfusion (benign oligemia). [64-65]

The DAWN hypothesis is that the greater the ratio of salvageable penumbra to infarct core (also referred to in the literature variously as "tissues at risk", "mismatch", and "target mismatch"), the higher the benefit is likely to be from reperfusion regardless of how much time has elapsed since stroke onset. In DAWN, we propose to select subjects for participation in the trial based upon a standardized identification and quantification of a "Clinical Imaging Mismatch". See **Section 5.2.5**.

5.2.1 Justification for Expansion of Time Window

In the dynamic setting of ischemia, there is continuous growth of the infarct core at the expense of the penumbral tissue until either the infarct is completed or reperfusion is achieved. The pace of expanding cerebral ischemia is highly variable between individuals and is likely dependent on multiple factors, including the presence of collateral circulation, ischemic pre-conditioning, cerebral perfusion pressure, and cerebral blood volume as well as serum glucose, body temperature, and oxygen delivery capacity.

MRI perfusion and PET studies suggest that the time point at which half of the patients with large vessel stroke show evidence of persistent penumbra is between 8 to 12 hours. [66] One MRI perfusion study demonstrated that as many as 70-80% of the patients with proximal arterial occlusion may have a significant mismatch as far as 9 to 24 hours post stroke onset. [37] In a retrospective study of 75 patients with acute ischemic stroke treated with endovascular recanalization therapies beyond 8 hours after symptom onset (baseline NIHSS 14 ± 4.9 and time to treatment 15.2 ± 8.7 hours), revascularization resulted in reduced infarct growth. The infarct growth was significantly greater when the baseline volume of infarct tissue was small and revascularization was not achieved. [67] Another retrospective study of patients selected by CT or MR perfusion mismatch who were treated endovascularly demonstrated similar rates of SICH, good outcomes and mortality whether treated at < 6 hours (N=34) or > 6 hours (N=21), concluding that in appropriately selected AIS patients endovascular therapy can be performed safely regardless of stroke duration. [68] These studies imply that the therapeutic window may be protracted in selected cases and support the hypothesis that it is possible to select subjects for endovascular therapy beyond 6-8 hours TLSW using advanced multimodal neuro-imaging.

Zaidi S. et al performed a retrospective analysis involving 160 consecutive patients with anterior circulation strokes undergoing endovascular therapy (IA tPA, angioplasty, stent and/or Merci Retriever) at a single institution (UPMC) over a five year period. Patients were divided into two groups according to TLSW to treatment: ≤ 8hr (n=123) and >8hr (n=37). All patients had <1/3 MCA territory hypodensity on baseline head CT and all patients treated >8 hours from TLSW had significant mismatch on MRI or CTP (by individual operator assessment). Except for a statistically significant difference in baseline

NIHSS, the two groups were well matched regarding baseline characteristics and site of occlusion. No significant differences were observed in rates of SICH, infarct volume or inpatient mortality. See Table 2 below. [44]

Table 2. Zaidi - Anterior LVOs treated ≤ 8 hrs and > 8 hrs after TLSW

	≤8hr (N=123)	>8hr (N=37)	p-value*
Baseline NIHSS (mean)	18	12	0.05
SICH (PH)	15.3%	8.3%	0.40
Infarct Volume	101.2 (96.3)	83.1 (64.6)	0.27
Inpatient Mortality	31%	20%	0.29

*Fisher exact test

In PROACT II, the largest randomized trial of anterior LVOs performed to date, time to treatment was not found to be a predictor of good clinical outcomes. [69] Conversely, the IMS I-II investigators found that, after adjustments were made for age, baseline NIHSS score, sex, and baseline glucose, only time from symptom onset to reperfusion and age independently predicted good clinical outcomes. [70] The authors concluded that at later times, reperfusion may be associated with a poor risk-benefit ratio. However, these findings are contradicted by a larger analysis involving the pooled dataset of the MERCI and Multi MERCI trials which demonstrated no association between time to treatment and outcomes or time to reperfusion and outcomes. [71]

Using the complete cohort of the prospectively collected "real world" Merci Registry subjects (N=1000), Nogueira RG, Jovin T et al. compared the outcomes of subjects with anterior circulation LVOs who underwent mechanical thrombectomy ≤ 8 hours to those who were treated > 8 hours from TLSW. [72] Earlier subjects were slightly older (67 vs. 63) and had higher baseline NIHSS scores (18 vs. 15) as compared to later subjects. There were no significant differences in terms of site of occlusion, recanalization rates, SICH rates, or good outcomes. Mortality was lower in the >8 hour group. The results of this comparison are summarized in Table 3**.**

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Table 3. Merci Registry - Anterior LVOs treated ≤ 8 hr and > 8 hr after TLSW

Outcomes	0-8 hours (n= 679)	>8 hours (n= 112)	Difference [95% CI]	p-value
Mean TLSW	4.7±1.5 hr	13.8±10.6 hr	n/a	n/a
Post-Rx TICI 2-3	78.9% (534/677)	81.3% (91/112)	-2.37% [-10.23%, 5.48%]	n/a
SICH Definite*	6.9% (33/477)	9.1% (7/77)	-2.17% [-8.99%, 4.64%]	n/a
SICH Uncertain*	2.1% (10/477)	5.2% (4/77)	-3.10% [-8.22%, 2.02%]	n/a
90-Day mRS 0-2	30.2% (205/679)	37.8% (42/111)	-7.65% [-17.31%, 2.01%]	0.12
90-Day Mortality	35.8% (243/679)	18.8% (21/112)	17.04% [8.96%, 25.12%]	0.0003

* Site reported according to the ECASS III criteria

One hypothetical reason that the subjects treated later in the Merci Registry did better than subjects treated earlier is due to more careful patient selection criteria being applied in the real world setting prior to intra-arterial interventions being initiated in this later time window. The results of this analysis further support that patients treated beyond 8 hours of symptom onset may experience similar rates of good clinical outcomes as those patients treated < 8 hours from symptom onset, and that they are not necessarily at higher risk of SICH, or death because of this treatment.

Jung et al compared prospectively collected data on endovascular treated stroke patients with known symptom onset < 6 hours to those with known symptom onset > 6 hours. Though outcomes in the cohort treated beyond 6 hours were worse than those treated within 6 hours, there were more patients with basilar artery occlusions in the latter group, and when multivariate regression analysis was performed correcting for this unequal distribution, the difference disappeared and outcomes were comparable. Recanalization rates were similar between the two groups, and hemorrhage rates were not increased in the patients who were treated later. [73]

In a retrospective analysis of 237 anterior LVO stroke patients, selected by CT Perfusion or MRI for endovascular treatment, Nogueira et al reported that neither time to treatment nor the use of adjunctive intra-arterial thrombolytics increased the risk for SICH. The overall recanalization rate (TIMI 2-3) was 74% (175/237), good outcomes at 90 days or discharge (mRS≤ 2) was 45% (100/223) and mortality was 21.7% (51/235). The overall SICH rate, defined as PH-1 or PH-2 per the European Cooperative Acute Stroke Study (ECASS) criteria, was 8.9% (21/237). Notably, there was no significant association between TLSW and SICH. [74]

A total of 169 patients from the original cohort discussed in the paragraph above met the main entry criteria initially planned for the DAWN trial including (1) baseline NIHSS score ≥10, (2) ICA or MCA-M1 occlusion (with or without cervical occlusion/severe stenosis), and (3) TLSW between 8-24 hours. This subset is also referred to as the "Pre-DAWN" dataset. Though not identical to the cohort described by the current study inclusion/exclusion criteria, it is similar enough to draw certain conclusions about potential outcomes in the proposed treatment arm.

The Pre-DAWN cohort achieved similar rates of revascularization, SICH, good outcomes, and mortality to the PROACT II Treatment Arm (N=121) despite having more severe occlusions (ICA terminus and tandem occlusions included, and M2 occlusions excluded) and significantly longer TLSW to treatment times. The Pre-DAWN cohort and the PROACT II Treatment arm both fared significantly better than the PROACT II Control arm. The results of this comparison are summarized on Table 4 below. [25, 38]

Clinical equipoise regarding potential benefit of neuro-thrombectomy in these subjects is well-established, as pivotal registration trials of neuro-thrombectomy devices did not include greater than 8 hour subjects and no randomized trial of any recanalization intervention has yet demonstrated benefit at this late time window. [75]

Table 4. Pre-DAWN Cohort vs. PROACT II Treatment and Control Arm

Variable	Pre-DAWN	PROACT II Treatment	PROACT II Control
Number of subjects	169	121	59
Age (years) Mean ± SD	64 ± 16	64 ± 14	64 ± 14
Median Baseline NIHSS (Min-Max)	17 (10 - 29)	17 (5 - 27)	17 (4 - 28)
Female	54%	42%	39%
TLSW to Treatment (Hr) Median (IQR)	12 (9.5-14.4)	4.7 (4.0-5.3)*	5.1 (4.2-5.5)
Site of Occlusion (%) MCA-M2 MCA-M1 ICA-T Tandem ICA/MCA Tandem ICA/ICA-T	 0% 54% 22% 17% 7%	 35% 61% 0% 0% 0%	 37% 63% 0% 0% 0%
Revascularization (TIMI 2-3)	74%	66%	18%
Symptomatic ICH	10%	10%	2%
90-day mRS ≤2	**40%** (57/142)	**40%**	**25%**
90-day Mortality	**25%** (42/167)	**25%**	**27%**

*Time to randomization

The preceding analyses support the hypothesis that endovascular recanalization therapies may be safely employed between 6-24 hours from witnessed or un-witnessed stroke onset or TLSW in appropriately selected subjects.

5.2.2 Justification for Inclusion of Wake up and Unclear Onset Strokes

It is estimated that 10-25% of ischemic stroke patients awaken with their deficits. [31, 33-36] In a study involving 100 subjects it was demonstrated that wake up stroke (WUS) subjects have similar DWI and PWI volumes to subjects with known stroke onset times. DWI-PWI mismatch was present in over 70% of the WUS subjects and MRA-detected vascular occlusion was documented in over 50% of the cases. [31] In another study, no significant difference was found in hyper-acute CT findings between 17 WUS subjects and 46 stroke subjects with known onset times when evaluated within 3 hours after stroke detection. [33]

Silva G. et al analyzed a prospectively acquired cohort of 676 consecutive subjects with AIS who underwent CTA within 24 hours of symptom onset, including 420 subjects with known onset time, 125 with unclear onset time, and 131 with WUS. The frequencies of LVO and CBF/CBV mismatch was not significantly different among the three groups, at 37%, 40.7%, and 37.1% respectively, suggesting that use of advanced neuro-imaging to determine the presence of LVO and mismatch may be particularly useful in this population. [32]

In contrast to the above findings, WUS subjects in the AbESTT-II trial experienced higher rates of symptomatic ICH (13.6% vs. 4%) and significantly lower rates of favorable outcomes (9.3% vs. 29.2%) as compared to non WUS subjects. However, in this trial the subjects were selected for inclusion based on a non-contrast head CT only, and the treatment arm subjects received IV abciximab. Of note, the rate of favorable outcomes among placebo-treated WUS subjects was lower than the placebo-treated non-WUS subjects, a finding that further highlights the need for more aggressive management of WUS patients. [34]

It is acknowledged that in the broadest cohort of AIS patients, as time from stroke onset increases so too does the risk to benefit ratio and not every patient will benefit, while some may be harmed by late reperfusion. [21, 38, 70] Many centers do not treat wake up or unclear onset strokes. Therefore, equipoise exists to randomize these subjects between endovascular treatment plus medical management or medical management alone.

The combination of advances in neuro-imaging acquisition and post-processing techniques and algorithms, and newer generation thrombectomy devices may enable these patients to be appropriately triaged for further therapy, thereby improving overall good clinical outcomes in this patient population.

5.2.3 Justification for Inclusion of IV tPA Failures

IV tPA has a short plasma half-life and its ability to revascularize large clot burdens is negligible. The recanalization rates of IV tPA for proximal arterial occlusions ranges from

only 10% for internal carotid artery (ICA) occlusions to 30% for proximal middle cerebral artery (MCA) occlusions. [76]

In earlier time windows it has been shown that combining IV tPA with neuro-thrombectomy does not substantially increase the risk of symptomatic intra-cerebral hemorrhage or other complications over that of neuro-thrombectomy alone. [77]

In subjects who are eligible, IV tPA should be administered as per the labeled indication and local practice guidelines, as this is considered best medical practice, and it should not be withheld from those who are eligible. However, if symptoms persist beyond 60 minutes after completion of IV tPA administration, and the presence of an intracranial ICA or MCA-M1 occlusion is confirmed by CTA/MRA, then the subject may be considered for eligibility in this trial.

If a subject presents to the participating site after having received IV tPA at an outside hospital, the participating site must repeat all relevant assessments, including the baseline NIHSS and CTA/MRA to confirm the presence of an occlusion in the intracranial ICA or MCA-M1, in order to qualify the subject as a potential candidate for participation in the trial. If the subject continues to meet all inclusion and none of the exclusion criteria they may be randomized and enrolled.

5.2.4 Justification for Non Reliance on Penumbra Imaging

Several studies have been reported in the literature demonstrating the general safety and effectiveness of using the ratio of "core infarct" to "salvageable penumbra" concept to select patients for reperfusion therapies. The methods of measuring and/or defining "core infarct" and "salvageable penumbra" however vary from study to study. [31, 37, 42, 78-83]

In DEFUSE 2, which included subjects within 12 hours from symptom onset, those with a "target mismatch" (favorable ratio of salvageable penumbra to infracted core tissue) who were reperfused, had an increased rate of good outcomes at 90 days compared to those who were not reperfused (57% vs. 31%). SICH rates were 7% vs. 19% respectively, suggesting that a randomized controlled trial of endovascular treatment for subjects with a target mismatch profile is warranted, [84] and does not expose subjects to an excessive risk of SICH.

The MR RESCUE trial used DWI-PWI mismatch to identify favorable penumbral patterns versus non-favorable penumbral patterns in subjects enrolled into the trial. Surprisingly, the trial failed to show a differential benefit of endovascular intervention among favorable penumbral pattern subjects. [59] However, the results are not definitive, given the small sample size, large core lesions at baseline, and modest rates of substantial recanalization. The results also raise the question of the validity of relying upon perfusion measurements to identify salvageable penumbra, as the perfusion study parameters used to categorize

favorable versus non favorable penumbral patterns in this trial failed to predict how much infarct growth would occur in the absence of reperfusion.

The STAIR VIII consensus statement recommends that in addition to vessel imaging to confirm large artery occlusion, full-scale penumbral imaging *should be* employed to select patients for possible inclusion into randomized therapy trials in the 8-24 hour timeframe, given the high proportion of subjects with already-completed infarcts. [75] However, there is no consensus in the literature on what the correct imaging modalities, maps or thresholds are for determining the extent of salvageable penumbra versus benign oligemia, versus already infarcted tissue. [85-86] Perfusion imaging is not yet a consistently reliable means of identifying salvageable penumbra. [87]

5.2.5 Justification for Use of Clinical Imaging Mismatch Criteria

Some data show that infarct core volume is a better predictor of outcomes than perfusion based imaging selection. [38, 88-89] DEFUSE 2 pre-procedure infarct volume along with age were the only independent predictors of outcome and core infarct volumes of less than or equal to 15 cc is the best discriminator of good versus bad outcome. Perfusion MR in addition to DWI did not add anything to this model. [90] In another retrospective analysis of 201 endovascularly treated patients, age and final infarct volume were found to be independent predictors of outcome. [91]

However, because patients with small core infarcts tend to do well even without treatment it is possible that infarct core by itself may not demonstrate a significant difference in outcomes between treated and a matched cohort of control subjects. The larger the mismatch between infarct core measurement and salvageable penumbra the greater the treatment effect is likely to be with reperfusion therapy, and the more substantial the infarct growth is likely to be without reperfusion therapy. No mismatch signals that the subject is not going to grow their infarct and thus will not benefit from reperfusion. [78, 82]

A Clinical Mismatch is the difference between the expected neurological deficits and the actual neurological deficits observed on examination of a patient, by National Institutes of Health Stroke Scale (NIHSS) in comparison to their occlusion location and size of core infarct. In the presence of small core infarct and confirmed LVO, baseline NIHSS appears to be a reliable indicator of "at risk" tissue. [87]

Patients with a low baseline NIHSS are likely to do well even in the presence of large vessel occlusion and no reperfusion therapy. In PROACT II there was a minimal treatment effect for M1 occlusions in the NIHSS 4-10 and a negative treatment effect for M2 occlusions in this same group (the control group did better). Larger treatment effects were noted both for M1 occlusions and M2 occlusions in the NIHSS 11-20 strata. [92]

Higher baseline NIHSS scores are generally well correlated with more proximal LVOs. In one study, NIHSS scores ≥10 demonstrated a positive predictive value for arterial occlusions in 97% of carotid and 96% of vertebrobasilar strokes. [93] In the EMS pilot study there was a significant correlation between the baseline NIHSS and the likelihood of presence of clot on initial angiography. All patients with a baseline NIHSS ≥15 and 44% of patients with NIHSS of 10 to 14 had appropriate clots. [94]

For subjects with a core infarct volumes between 0 and 30 cc, a baseline NIHSS cutoff of ≥10 was chosen to define the clinical imaging mismatch because it is thought to be a reasonable predictor of likely progression of stroke and/or poor outcome in the absence of reperfusion. [95]

For subjects with larger core infarct volumes, above 30 cc but less than 50 cc, a baseline NIHSS cutoff of ≥20 was chosen to define the clinical imaging mismatch, based upon this same subgroup of subjects in IMS III. Though not statistically significant at the p=0.05 level, the group treated with endovascular therapy had a higher rate of good clinical outcomes compared to the IV tPA group (23.8% versus 16.8% respectively). [58]

Stricter inclusion criteria are defined for subjects greater than 80 years of age. In one study of IV tPA treated patients, the overall rate of symptomatic ICH (SICH) in the octogenarians was 6.9%, compared with 5.3% in younger patients. The use of MRI to select octogenarians for thrombolytic therapy seemed to decrease the risk of SICH, but did not influence the overall outcome after 3 months. [96] In another published study comparing outcomes in IV tPA treated and non-treated subjects ≥ 80 and < 80 years old, although age was associated with poorer outcomes the association between thrombolysis treatment and improved outcomes was maintained in the very elderly subjects, and their conclusion is that age alone should not be considered a barrier to treatment.[97] However, in order to mitigate the potential risks associated with endovascular treatment in the elderly as well as to maximize the chance of a good outcome, the core infarct volume in subjects who are ≥ 80 years will be restricted to ≤ 20 cc.

In the absence of a "gold standard" to define salvageable penumbra, DAWN subject selection is based on a Clinical Imaging Mismatch using standardized collection and post processing of MRI-DWI or CTP-rCBF maps to calculate core infarct volumes, across all study sites.

A Clinical Imaging Mismatch is the observed difference between the size of the core infarct and the magnitude of the neurological deficit, in the presence of confirmed LVO by CTA/MRA, and appears to be a reliable and efficient surrogate for assessing salvageable penumbra. [87] Using this method we aim to select subjects at risk of further infarct growth without rapid reperfusion.

Based upon the above justifications, there are three distinct Clinical Imaging Mismatch subgroups defined in DAWN:

a. 0-<21 cc core infarct and NIHSS ≥ 10 (and ≥ 80 years old)
b. 0-<31 cc core infarct and NIHSS ≥ 10 (and < 80 years old)
c. 31 cc to <51 cc core infarct and NIHSS ≥ 20 (and < 80 years old)

5.2.6 Justification for Use of Standardized Core Infarct Imaging Software

In order to select subjects who are most likely to benefit from mechanical thrombectomy and less likely to be harmed by it, the inclusion criteria are limited to subjects with core infarct volumes between 0-50 cc. In DAWN, core infarct volume measurements will be standardized using a validated, FDA-cleared software platform for measuring core infarct (RAPID software, iSchemaView, Palo Alto, CA, or alternatively Olea Sphere, Olea, Cambridge, MA)

Diffusion/perfusion imaging software for core infarct assessment is 510(k) cleared in the United States, and has been/is being used in several global stroke trials to date, including DEFUSE, DEFUSE 2, EXTEND, EXTEND IA, CRISP, and SWIFT PRIME. The software takes DICOM images acquired on a variety of CT or MR scanners and uses an automated algorithm to post-process the resulting ADC maps (MRI-DWI) or r-CBF maps (CTP) in order to consistently measure core infarct volumes. All raw data/maps will be visible to the treating physician such that if an artifact or error is suspected the scans can be assessed visually to confirm that the patient is appropriate for enrollment.

The CT/MR Core Lab will verify, and record, the core infarct volumes generated by the software as well as "cleaned" volumes following removal of any artifact. The core lab will also provide timely feedback to the study sites regarding quality control issues.

Since it is recognized that any image of the brain is a “snapshot in time”, DAWN requires that the corresponding clinical “mismatch” be evaluated using the baseline NIHSS obtained within 1 hour of the processed images used to qualify the subject for the study.

Though MRI-DWI is the preferred method to measure the core infarct volume, due to logistic barriers such as unavailability of MRI equipment or technicians, and subject contra-indications for MR, sites are permitted to use either MRI-DWI or CTP-rCBF to measure the core infarct volume.

5.2.7 Justification for Use of Weighted mRS as Primary Endpoint Analysis

The primary endpoint is 90-day clinical outcomes assessed by the modified Rankin Scale (mRS), analyzed using both the average weighted mRS categories (weighted mRS

analysis) and proportions of subjects with good functional independence (mRS 0-2) (dichotomous analysis).

It is possible that widespread use of dichotomized outcome scales can potentially lead to the discarding of important information about treatment effects. Analysis over ranks, taking into account all assessed gradations of outcome along the disability spectrum, provides a more comprehensive assessment of intervention effects and has been recommended by both the US and European consensus expert groups on trial design. [98-99]

An important advancement is the development of utility values for each level of the modified Rankin Scale of global disability. [75] Weighting the seven Rankin levels by utilities further improves the precision of the scale as a measure of disability, converting the scale from a somewhat arbitrary fixed interval instrument to a measure with rank distances that directly reflect patient and society valuation of outcome health states. Formal derivations of utility values for each Rankin grade has recently been completed by two groups, using patient informants from a population-based study and using health professional informants following the World Health Organization Global Burden of Disease methodology. [48,49] Both methods yielded similar values, which were averaged to derive the utility-weighted Rankin Scale used in this trial. Use of a utility-weighted Rankin Scale permits a trial to capture all the effects a treatment can have on a subject to the degree each is important to the subject and society [104].

5.2.8 Justification for Use of Adaptive Design

The combined feasibility / pivotal design increases trial efficiency, allowing the study to be stopped early if there is no evidence of a meaningful treatment effect, or allowing it to continue if a meaningful treatment effect is perceived after the first interim analysis. The adaptive design allows for early and frequent interim analyses so that rather than waiting until the maximum number of subjects have been enrolled, decisions about stopping early for either predicted success or failure, are made based on pre-specified rules and patients are spared from unnecessary randomization.

The adaptive design also allows for refinement of the target population to smaller infarct sizes based on the data that accumulates during the course of the trial, thereby sparing the randomization of future subjects who are unlikely to benefit from the treatment. Refer to **Appendix F**, which contains the Adaptive Design Plan, prepared by Berry Consultants.

Currently there is clinical equipoise to randomize subjects between these two arms because there is no evidence of improved clinical outcome in patients who are treated either way within 6-24 hours from time last seen well. Adaptive trial design techniques may be helpful in identifying subgroups of subjects with enhanced treatment benefit and delineating the thresholds at which benefits fade. Several biomarkers have been identified that are hypothesized to identify patients with substantially increased benefit from neuro-thrombectomy, including infarct core size, presence of salvageable penumbra, etc. A

Bayesian adaptive trial design permits information gained about subgroups collected within the trial to modify enrollment criteria as the study progresses. [100] The core volume threshold at which benefit no longer accrues, if one exists, is likely to be most efficiently identified by using adaptive modification of trial entry criteria. [75]

5.3 Method of Assigning Subjects to Treatments

Randomization will be accomplished at each site using either a block of randomization envelopes, or by using a commercially available Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). Subjects will be randomized 1:1 to Trevo thrombectomy plus medical management or medical management alone. In order to ensure both groups are balanced, subjects will be stratified by Clinical Imaging Mismatch (CIM) subgroups (see Imaging Inclusion Criteria in **Section 6.1.1**), TLSW between 6 and ≤ 12 hours and >12 to 24 hours, and baseline occlusion location (ICA vs. M1). Enrollment in this study is defined as the moment when the randomization process is completed and the subject is assigned to a study arm. **After randomization, no crossover is permitted.**

5.4 Blinding and Breaking the Blind

This protocol is designed as an open label treatment assignment. The presence or absence of hemorrhage will be determined by the CT/MR core lab which is blinded to each subject's group assignment. Core infarct volume at baseline will be measured by automated calculations, using standardized software at each participating site. Review of all images and calculations will be conducted by the CT/MR core lab on an ongoing basis as images are collected (within 72 hours will be the goal), and feedback will be provided to the sites to ensure that the Core Infarct volumes are not impacted by artifacts or equipment upgrade issues at the site. The Angiographic Core Lab assessing angiograms for revascularization/reperfusion will not be blinded, as this evaluation will only be made for subjects in the Trevo Thrombectomy plus medical management arm.

Each site must designate one or more individual(s) to perform the blinded mRS assessments at Day 5-7 or discharge (whichever is earlier), Day 30 (±14) and Day 90 (±14). This individual will be identified on the Delegation of Authority Log, and must not perform data entry or other tasks that would reveal the study arm assignment of subjects. Moreover, the blinded evaluator(s) will be instructed to follow a scripted interview to minimize the chance of subjects disclosing their treatment group to the evaluator, and will also be required to self-certify that they remained blinded throughout the interview with the subject. If the blind is broken for any reason, this will be documented on the data collection forms.

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6 Study Population

6.1 Inclusion Criteria

General Inclusion Criteria	1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups: a. Subject has failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration) b. Subject is contraindicated for IV t-PA administration 2. Age ≥18 3. Baseline NIHSS ≥10 (assessed within one hour of measuring core infarct volume) 4. Subject can be randomized between with 6 to 24 hours after time last known well 5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1) 6. Anticipated life expectancy of at least 6 months 7. Subject willing/able to return for protocol required follow up visits 8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form* * If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient utilizing emergency informed consent procedures if neither the patient nor the representative or person of trust is available to sign the informed consent form. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research. (Not applicable to U.S. Sites.)
General Inclusion Criteria (additional information)	1. Subjects receiving heparin or low molecular weight (LMW) heparin e.g. Fragmin® (Dalteparin Sodium) or an intravenous direct thrombin inhibitor such as Angiomax® (Bivalirudin), or Argatroban within the last 24 hours from screening are eligible for participation if their coagulation profile remains acceptable. 2. Subjects on factor Xa inhibitors (e.g. apixaban) or direct thrombin inhibitors are eligible for participation
Imaging Inclusion Criteria	1. < 1/3 MCA territory involved, as evidenced by CT or MRI 2. Occlusion of the intracranial ICA and/or MCA-M1 as evidenced by MRA or CTA 3. Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps: a. 0-<21 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old) b. 0-<31 cc core infarct and NIHSS ≥ 10 (and age < 80 years old) c. 31 cc to ≤51 cc core infarct and NIHSS ≥ 20 (and age < 80 years old)

6.2 Exclusion Criteria

General Exclusion Criteria	1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history 2. Rapid improvement in neurological status to an NIHSS <10 or evidence of vessel recanalization prior to randomization 3. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. dementia with prescribed anti-cholinesterase inhibitor (e.g. Aricept) 4. Seizures at stroke onset if it makes the diagnosis of stroke doubtful and precludes obtaining an accurate baseline NIHSS assessment 5. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol)

	6. Baseline hemoglobin counts of <7 mmol/L (11.28 g/dL) 7. Baseline platelet count < 50,000/uL 8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L 9. Renal failure as defined by a serum creatinine >3.0 mg/dL (264 µmol/L) NOTE: subjects on renal dialysis may be treated regardless of serum creatinine levels 10. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal. NOTE: Patients on factor Xa inhibitor within 24-48 hours must have PTT within 3 times normal. 11. Any active or recent hemorrhage within the past 30 days 12. History of severe allergy (more than rash) to contrast medium 13. Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg) NOTE: If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled 14. Female who is pregnant or lactating at time of admission 15. Current participation in another investigational drug or device study 16. Presumed septic embolus, or suspicion of bacterial endocarditis 17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	1. The "correction" of baseline glucose or coagulation laboratory values to meet inclusion criteria will not be allowed. 2. Subjects who have taken Clopidogrel, aspirin, or both within the last 24 hours from screening for the trial should not be excluded if their coagulation profile remains acceptable. 3. Subjects with a questionable seizure at onset of stroke should not be excluded if CTA/MRA confirms the presence of intracranial ICA and/or M1 occlusion, and accurate NIHSS can be obtained.
Imaging Exclusion Criteria	1. Evidence of intracranial hemorrhage on CT/MRI 2. CTA or MRA evidence of flow limiting carotid dissection, high-grade stenosis, or complete cervical carotid occlusion requiring stenting at the time of the index procedure (i.e., mechanical thrombectomy). 3. Excessive tortuosity of cervical vessels on CTA/MRA that would likely preclude device delivery/deployment 4. Suspected cerebral vasculitis based on medical history and CTA/MRA 5. Suspected aortic dissection based on medical history and CTA/MRA 6. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device 7. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior circulation/vertebrobasilar system) as confirmed on CTA/MRA, or clinical evidence of bilateral strokes or strokes in multiple territories 8. Significant mass effect with midline shift as confirmed on CT/MRI 9. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI

6.3 Withdrawal and Replacement of Subjects

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional follow-up, nor will they be replaced.

6.4 Enrollment Controls

Enrollment will be monitored to ensure that no more than the maximum planned number of subjects is enrolled. An electronic data capture system will be used, and the system will be set to automatically notify the CRA or Project Manager of all subject enrollments being entered within the system. As enrollment nears the maximum allowed one of two methods will be employed to notify sites of status of enrollment:

1. If an automated randomization system is utilized, sites will be notified via automatic pre-programmed notifications within the IVRS/IWRS system, when they attempt to randomize a patient, specifically when enrollment is no longer available.

2. If randomization envelopes are utilized, the Project Manager or designee will monitor the enrollment status daily (when enrollment is within 10 subjects of the maximum allowed enrollment) and send out an e-mail requesting sites to call a specific telephone number or e-mail a designated person to ask permission before randomizing and enrolling a subject.

7 Study Procedures

The schedule of events is the same for all subjects in the trial except those subjects randomized to the Trevo plus Medical Management arm will undergo an intra-arterial Trevo thrombectomy procedure. All subjects who are enrolled into the trial will be followed for 90 days (± 14) unless they withdraw early from the trial, expire before the 90 day follow up window is reached, or are lost to follow up. The Time and Events schedule is outlined in Table 5.

7.1 Written Informed Consent

Written Informed Consent must be obtained for all subjects who are screened and meet the general inclusion/exclusion criteria prior to randomization/enrollment.

Note - If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient utilizing emergency informed consent procedures if neither the patient nor the representative or person of trust is available to sign the informed consent form. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research. (Not applicable to U.S. Sites.)

The subject or the subject's Legally Authorized Representative (LAR) will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed. The Informed Consent Form (ICF) must be approved by the study Institutional Review Board

(IRB)/ Ethics Committee (EC). For U.S. Sites, electronic informed consent procedures may be utilized if approved by the IRB and consistent with FDA guidance on use of electronic informed consent in clinical investigations.[1] Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent Form, non invasive baseline imaging or cerebral angiography may demonstrate that the subject is not a suitable candidate for the assigned study treatment.

A Screening and Enrollment Log will be maintained by the site to document basic information such as date screened and reason for screen failures for subjects who fail to meet the study eligibility criteria. Screen failed subjects and their reason(s) for screen failure will be documented and may be entered into the electronic database, but they will not be followed beyond the screening visit, and no further data will be collected/recorded.

7.2 Prior to Randomization

The following pre-procedure data must be collected before randomization and enrollment for all subjects (and before the index procedure for those subjects randomized to the Trevo Thrombectomy plus medical management arm):

- Confirmation that all inclusion and none of the exclusion criteria have been met
- Demographics and medical history
- Neurological examination
- Platelets/Hemoglobin
- PT/PTT/INR
- Blood glucose
- Sodium concentration
- Potassium concentration
- Serum creatinine
- Pregnancy test (required for females of child bearing potential; not required for females who are surgically sterile or post-menopausal)
- MRI/MRA or CT/CTA/CTP (if MR is contra-indicated or unavailable) to assess for hemorrhage, confirm the presence of an anterior large vessel occlusion in the ICA or MCA-M1 arteries, and to measure the core infarct volume

To facilitate consistency and clarity, a time standard is established for this study, with time zero "t = 0" defined as the time of randomization, which occurs after initial MRI/MRA or CT/CTA/CTP to assess for hemorrhage, confirm the presence of an anterior large vessel occlusion in the ICA or MCA-M1 arteries, and to measure the core infarct volume. Baseline is defined as the period of time from initial stroke admission up to time of randomization.

[1] Food and Drug Administration. Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers. Guidance for Industry. Draft Guidance issued March, 2015.

All subsequent time points (e.g. 24-hours, Day 5-7, Day 30 and Day 90) will be in reference to time of randomization (time zero). Refer to Table 5, DAWN Study Time and Events Schedule, for all required tests and time windows (with allowed ranges). The following time references will be used in this study during the screening phase:

- **Time Last Seen Well** - This is the time the subject was last seen (or known to be) well in "wake-up" stroke cases or the time that subject's symptoms were first noticed in witnessed stroke cases.
- **Time of symptom onset** – This is the time that subject's symptoms were first noticed for subjects with witnessed events.
- **Time of treatment initiation –** In the treatment arm treatment is considered to have begun at the time of access site puncture; in the control arm it is the time of randomization.

All subjects enrolled/randomized into the trial will be categorized as one of the following:

- Wake-up Stroke: Subject known to have symptoms first detected on awakening from sleep.
- Witnessed Stroke: Subject last known well time and symptoms first observed time known to be the same.
- Un-witnessed Stroke: Subject last know well time and symptoms first observed time known to be different, but not known to have symptoms first detected on awakening from sleep.

For the purposes of trial enrollment the subject must have a thrombus identified within the intracranial ICA, and/or MCA-M1 arteries by pre-procedure MRA or CTA. The MCA-M1 segment is defined as the first branch of the intracranial ICA which courses horizontally from its branching point off the ICA through the sylvian fissure up to the first bifurcation distal to the lenticulostriate arteries, in the Sylvian fissure.

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Table 5. DAWN™ Trial Time and Events Schedule

Event	Screening/ Baseline	Procedure (Treatment Arm Only)	24 Hr (-6/+24) (post randomization)	Day 5-7 / Discharge (whichever is earlier)	Discharge	Day 30 ± 14	Day 90 ± 14
Inclusion/Exclusion Criteria	✔						
Demographics/Medical History/Baseline Medications	✔						
Baseline Characteristics	✔						
Baseline Labs	✔						
Informed Consent	✔						
Randomization (= time zero)	✔ ††						
Angiography Procedure Details (Treatment Arm only) ***		✔					
mRS †	✔ (pre stroke)			✔ †		✔ †	✔ †
NIHSS	✔ *		✔ **	✔		✔	✔
Neuro imaging (to assess for hemorrhage, occlusion location/vessel patency & infarct volume)***	✔ MRI/MRA or CT/CTA/CTP		✔ MRI/MRA or CT/CTA	✔ MRI or CT (optional)			
AEs/SAEs (from time of randomization)		✔	✔	✔	✔	✔	✔
Concomitant Medications		✔	✔	✔		✔	✔
In Hospital Med Management					✔		
Intubation Details					✔		
UB04 / Health Economics					✔		

*NIHSS within 1 hour of corresponding core infarct measurement.
** NIHSS should be obtained within approximately 2 hours of the 24 (-6/+24) hour neuro-imaging to determine presence/absence of hemorrhage.
† mRS must be conducted by an individual blinded to the treatment arm.
†† Randomization should occur within 1 hour of obtaining neuro imaging used to determine core infarct measurement.
*** CT/MR and Angiographic images should be de-identified before being submitted to Stryker NV or core lab.

7.3 Angiography Procedure (Treatment arm only)

7.3.1 Diagnostic Angiography

For the subjects randomized to the Trevo Thrombectomy plus medical management arm, treatment initiation is defined as the date and time of arterial access. Arterial Access using appropriate anesthesia, should be obtained per standard practice at the treating institution, and should be obtained **within 60 minutes of randomization**. Treatment initiation, defined as time of access site puncture, must occur after six hours, but before 24 hours since the subject was last seen well.

A diagnostic angiogram must be performed in order to determine the appropriateness of the occlusion for treatment with the Trevo Retriever. The occlusion location(s) will be recorded by the site on the appropriate CRF. Angiographic evaluations will be done before Trevo device use, after Trevo device use, and post procedure to determine vessel patency as well as the presence of embolization to new territory (ENT) or distal emboli (DE), and contrast extravasation (a sign of hemorrhage). Angiography must be performed in the involved territory. If angiographic images are missing from the sequence of acquisitions, the core lab will request the site to resend the entire angiography dataset.

Embolization to new territory (ENT) is defined as any new infarct on CT or DWI at 24 (-6/+24) hours compared to baseline CT or MRI in the ipsilateral ACA for MCA occlusions. Any new neurological deficit not referable to the affected hemisphere occurring post intervention with or without MRI lesion equivalent will also be adjudicated as embolization to new territory. ACA infarcts ipsilateral to a carotid terminus occlusion will not be considered as a procedure-related adverse event unless no infarct is seen on baseline DWI. Any new vessel occlusions in previously unaffected territories including ACA ipsilateral to a carotid terminus occlusion if absent on the baseline DWI will be considered procedure related.

If the suspected distribution of ischemia is in the anterior circulation, a contrast injection into the common carotid artery to examine the carotid bifurcation and intracranial arteries should be performed. If an occlusion is identified, with failure to visualize the terminal internal carotid artery, the opposite carotid artery and/or vertebral artery should be injected to identify collaterals across the Circle of Willis pial collateral blood supply and patency of the ACA and MCA unless catheterization of the contralateral carotid artery would pose unacceptable procedural risk or significant delays.

Prior to the start of the procedure, the modified TICI scores within the vascular territory being treated should be assessed. Angiographic films of the occlusion being treated must allow clear visualization of the target artery. The same orientation should be used before and after the Trevo Thrombectomy in order to allow a valid analysis of the reperfusion status of the vessel(s). The late venous phase should be included in all angiogram

acquisitions. Sites should submit all angiographic data to the Core Lab, rather than pre-selecting a subset of images. If angiographic images are missing from the sequence of acquisitions, the core lab will request the site to resend the angiography dataset.

In the event of a procedural complication or adverse event, detailed angiographic images should be obtained and submitted. All adverse events that occur during the procedure must be documented and recorded on the applicable CRFs.

7.3.2 Unexpected Diagnostic Angiography Findings

One of the main inclusion criteria for the study is the presence of an Intracranial ICA and/or MCA M1 segment occlusion on the pre-randomization CTA/MRA. Subjects with isolated proximal cervical ICA occlusions, isolated M2 occlusions, and subjects with occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) on the pre-randomization CTA/MRA are excluded from the study. Given the high accuracy of CTA/MRA in detecting proximal intracranial occlusions we expect near perfect correlation with the findings on conventional angiography. However, the following unexpected situations may arise:

A. If there is no thrombus in any treatable vessel on the initial diagnostic angiography (e.g. Intracranial ICA with or without MCA involvement, or MCA M1) no Trevo device will be used and the procedure will be terminated.

   After review of the multimodal CT/MRI and Angiograms by the Core Labs, the data from these cases will be analyzed according to one of the following rules:

   1. If the occlusion (enrollment criteria) was misdiagnosed by the enrolling center on the initial CTA/MRA evaluation (as per CT/MR Core Lab determination), this will be considered a major protocol violation and these subjects will be analyzed in the "intent-to-treat" analysis, but not the "per protocol" analysis, utilizing their "actual" mRS score as the primary outcome measure.
   2. If a treatable occlusion was present on the initial CTA/MRA evaluation (as per CT/MR Core Lab determination) but is not visualized on the baseline diagnostic Angiogram by the Angiographic Core Lab, these subjects will be categorized as having achieved spontaneous recanalization and will be analyzed in both the "intent-to-treat analysis" and the "per protocol" analysis, utilizing their "actual" mRS score as the primary outcome measure.

      Additional sensitivity analyses will be performed excluding subjects who do not receive the assigned therapy.

B. If thrombus is identified in one or more proximal non treatable arteries per protocol and in none of the per-protocol treatable arteries on the initial diagnostic angiography (e.g. Proximal cervical ICA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), vertebral artery (VA) or basilar artery (BA)) these occlusions may be treated as per local standards and guidelines. After review of the multimodal CT/MRI and Angiograms by the Core Labs, the data from these cases will be analyzed according to one of the following rules:

1. Except for a core lab adjudicated M2 occlusion that is considered M1 occlusion by the local investigator, if the occlusion location (enrollment criteria) was misdiagnosed by the enrolling center on the initial CTA/MRA evaluation (as per CT/MR Core Lab determination), this will be considered a major protocol violation and these subjects will be analyzed in the "intent-to-treat" analysis, but not the "per protocol" analysis, utilizing their "actual" mRS score as the primary outcome measure.
2. Except for a core lab adjudicated M2 occlusion that is considered M1 occlusion by the local investigator, if there is a new occlusion present in a non treatable vessel per protocol that was not present on the initial CTA/MRA evaluation (as per CT/MR Core Lab determination), this will be considered a Procedure-related serious adverse event (e.g. Embolization to a new territory) and these subjects will be analyzed in both the "intent-to-treat" analysis and the "per protocol" analysis, utilizing their "actual" mRS score as the primary outcome measure.

   Sensitivity analyses will be performed excluding subjects who do not have a protocol specified lesion and are treated off protocol with any device.

C. If thrombus is identified in one or more distal non treatable arteries, per protocol (e.g. the ipsilateral M2 or M3 MCA segment), and none of the per protocol treatable arteries on the initial diagnostic angiography, and the occlusion in the opinion of the physician caring for the subject could potentially lead to major disability it may be treated as per the local management guidelines.

   After review of the multimodal CT/MRI and Angiograms by the Core Labs, the data from these cases will be analyzed according to one of the following rules:

1. If the occlusion location (enrollment criteria) was misdiagnosed by the enrolling center on the initial CTA/MRA evaluation (as per CT/MR Core Lab determination), this will be considered a major protocol violation and these subjects will be analyzed in the "intent-to-treat" analysis, but not the

"per protocol" analysis, utilizing their "actual" mRS score as the primary outcome measure.

2. If a treatable occlusion was present on the initial CTA/MRA evaluation (as per CT/MR Core Lab determination), but is not visualized on the baseline diagnostic Angiogram by the Angiographic Core Lab, these subjects will be categorized as having achieved spontaneous recanalization with distal clot migration and will be analyzed in both the "intent-to-treat analysis" and the "per protocol" analysis, utilizing their "actual" mRS score as the primary outcome measure.
   Sensitivity analyses will be performed excluding subjects who do not have a protocol specified lesion and are treated off protocol with any device.

Of note, for randomized subjects who meet clinical, imaging and laboratory criteria for entry into the study and who are randomized to the treatment arm, but who are not treated with endovascular therapy due to spontaneous recanalization or other factors (inability to access the lesion, etc.) the subject is considered enrolled and the site must still follow the subject through 90 days and collect all relevant data.

7.4 Trevo Thrombectomy Procedure (Treatment arm only)

In subjects randomized to the Trevo thrombectomy plus medical management arm, the procedure should be performed using only the Trevo Retriever. If for any reason, the Trevo Retriever cannot be used, the subject will still be analyzed in the Trevo Thrombectomy plus medical management arm in an intent-to-treat (ITT) analysis.

NOTE: The procedure must be started (defined as the time of arterial access) no earlier than 6 hours, but before 24 hours, from the time of symptom onset or the Time Last Seen Well (TLSW). This is when treatment is considered to be initiated in this group.

The interventional procedure should be completed within two (2) hours of arterial access.

Heparin anticoagulation may be used but should not exceed a total of 2,000 units of Heparin bolus followed by 500 units/hour Heparin drip for the duration of the procedure.

Prudent use of anti-vasospasm agents is permitted.

Use of the Trevo device should be terminated if there is any angiographic evidence leading to the suspicion of an intracranial hemorrhage, such as extravasation of contrast during the procedure.

Physicians should follow the most current Instructions for Use (IFU) at all times with regards to the device compatibility, preparation and the recommended retrieval procedure. Key preparation and procedure steps are described below:

1. Using conventional catheterization techniques, place Microcatheter into target vessel using a standard neurovascular guidewire. Anatomy permitting, position Microcatheter tip distal to thrombus.
2. Important: If insertion tool is not properly flushed, it may be difficult to advance the Retriever through the insertion tool.
3. Advance Retriever until distal tip aligns with tip of Microcatheter. **Note**: Retriever tip will be within 15 cm of exiting Microcatheter tip when (a) distal end of Retriever shaft marker reaches Microcatheter hub, or (b) proximal end of Retriever shaft marker reaches proximal end of rotating hemostasis valve.
4. Retract Microcatheter while applying gentle forward force to Retriever to deploy shaped section of Retriever within clot. Position Microcatheter tip marker just proximal to shaped section of Retriever.
   Warning: To reduce risk of fracture, maintain Microcatheter tip marker just proximal to shaped section of Retriever during manipulation and withdrawal.
5. After deploying Retriever, allow sufficient time for clot to integrate into the Retriever (approximately 5 minutes).
6. If using a Balloon Guide Catheter, inflate balloon to occlude vessel as specified in Balloon Guide Catheter labeling.
7. Position and lock torque device onto Retriever at Microcatheter hub.
8. Slowly withdraw Retriever and Microcatheter as a unit to Balloon Guide Catheter or Guide Catheter tip while applying aspiration to Guide Catheter using 60 mL syringe.
9. Apply vigorous aspiration to Balloon Guide Catheter or Guide Catheter using 60 mL syringe and withdraw Retriever and Microcatheter inside Guide Catheter. Continue aspirating until Retriever and Microcatheter are nearly withdrawn from Guide Catheter. Note: If withdrawal into Balloon Guide Catheter or Guide Catheter is difficult, deflate Balloon Guide Catheter balloon and simultaneously withdraw Guide Catheter, Microcatheter and Retriever as a unit through sheath. Remove sheath if necessary.
10. Deflate Balloon Guide Catheter balloon.
11. Disconnect Guide Catheter rotating hemostasis valve and fully remove Retriever, Microcatheter and rotating hemostasis valve as a unit from Guide Catheter.
12. Clean the device with saline. Inspect Retriever for damage. Do not reuse Retriever if core wire, shaped section or platinum coil appears different than when first removed from package. If not damaged, the Retriever may be used for up to three (3) retrieval attempts. A retrieval attempt is one (1) advancement and complete withdrawal cycle.

Warning: Do not perform more than six (6) retrieval attempts in the same vessel using Retriever devices. This total number applies for any combination of retrieval devices.

Immediately after each retrieval attempt with the Trevo Retriever, perform biplane angiography in order to assess the vessel patency in the neurovascular tree that is being treated. Angiography should include ipsilateral AP and lateral imaging of the involved arterial system, including potential collateral vessels.

a. If reperfusion has been successful with the Trevo Retriever (defined as at least **TICI 2b**(reperfusion of > 2/3 MCA territory) in the territory treated) the Trevo thrombectomy procedure should be stopped and no further interventions performed.

b. If reperfusion has not been successful with the Trevo Retriever (defined as modified **TICI 0-2a** in the territory treated) continue with additional retrieval attempts (up to the maximum allowed per the IFU). Adjunctive treatment (rescue therapy) may be initiated after the 6 passes if deemed appropriate by the treating physician, but it is discouraged as it constitutes a major protocol violation and its clinical benefit is unclear.

Adjunctive therapy (e.g. use of another stent retriever or stent) is strongly discouraged and represents a major protocol violation. Participants who receive rescue adjunctive therapy will be imputed as mRS=6. If adjunctive treatment (rescue therapy) is used AFTER the Trevo Retriever, biplane angiography should be performed immediately afterwards in order to reassess vessel patency and determine the effect of the adjunctive rescue treatment. Angiography should include ipsilateral AP and lateral imaging in the involved arterial system, including potential collateral vessels. This information will be used to quantify the overall procedural reperfusion rates after the use of the Trevo Retriever versus at the end of the procedure.

NOTE: The last angiogram prior to the use of rescue therapy will be considered when rating post-Trevo Retriever reperfusion. However, use of any intra arterial lytic or intra-arterial antiplatelet agent, or other mechanical devices, during or after the Trevo Retriever will automatically categorize the subject as a Trevo revascularization "failure" regardless of their revascularization status prior to the rescue therapy. Therefore interventionalists will be discouraged from using intra arterial lytics or antiplatelets, or other mechanical devices during the procedure, unless it is deemed that not performing rescue therapy will put the subject at more significant risk than by performing rescue therapy. Use of rescue therapy will be considered a protocol violation.

7.5 End of the Trevo Thrombectomy Procedure (Treatment arm only)

The Trevo thrombectomy procedure should be terminated if any of the following occur:

1. Neurological deterioration or alteration in function is detected leading to the suspicion of an intracranial hemorrhage
2. The time from groin puncture reaches 2 hour
3. TICI grade 2b or 3flow (reperfusion of > 2/3 MCA territory) is established
4. The occlusion is refractory to six retrieval attempts in a single vessel

Neurological deterioration or alteration in function leading to the suspicion of an intracranial hemorrhage will necessitate an emergent head CT or MRI scan. At the discretion of the investigator, this evaluation may also include angiography or other diagnostic tests to

determine the etiology of the clinical alteration. Management of an intracranial hemorrhage will be performed according to each institution's usual practice.

7.6 24 (-6 / +24) Hours post Randomization

The following data will be collected at 24 (-6/+24) hours post randomization:

- In hospital medical management details
- NIHSS
- MRI/MRA or CT/CTA in order to assess for hemorrhage, vessel patency and infarct core volume. The same imaging modality should be used at 24 (-6/+24) hours to measure vessel patency as was used at baseline to identify occlusion location. MRI T2 Flair or CT may be used to assess core infarct volume.
- Adverse events and any treatment administered

For all subjects who expire prior to the 24 (-6/+24) hour assessment, available information regarding the primary cause of death and date/time of death will be recorded, as well as whether the subject was made "do not resuscitate" (DNR) or "comfort care only" prior to expiration.

Deaths MUST be reported to Stryker NV within 24 hours of becoming aware, preferably by CRF completion. In the event that the EDC system is unavailable a written report by e-mail or fax is acceptable.

7.7 Concomitant Medications and Management

Treatment Arm:

- Use of IV or IA lytics, or IA antiplatelets is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed.
- Systemic anticoagulation with heparin may be used during the procedure, but should not exceed a total of 2,000 units of heparin bolus followed by a 500 units/hour drip for the duration of the procedure.
- Prudent use of anti-vasospasm agents is permitted during the procedure.

Medical Management Arm:

- IV heparin is prohibited until after the 24 (-6/+24) hour neuro-imaging has been performed to determine the presence/absence of intracranial hemorrhage.
- The administration of medications is at the treating physician's discretion according to local standards of care, but may NOT include any intra-arterial therapies.

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Both Arms:

- Newly administered aspirin (IV or oral) and/or Clopidogrel are the only anti-platelets allowed within the first 24 hours post randomization, until after the 24 (-6/+24) hour neuro-imaging has been performed to determine the presence/absence of intracranial hemorrhage.
- Subjects previously treated with antiplatelet agents or combination antiplatelet therapy (e.g. for a previously implanted drug eluting stent), may continue this regimen if in the investigator's opinion the benefits of continued therapy outweigh the risks of potential neurological deterioration related to hemorrhage.
- Subcutaneous Low Molecular Weight (LMW) heparin is allowed for Deep Vein Thrombosis (DVT) prophylaxis per the center's standard of care.
- All subjects enrolled into this study should be medically managed according to the 2013 AHA guidelines, and specifically as follows with regards to blood pressure and glucose management.[29]

7.7.1 Blood pressure management

The management of arterial hypertension remains controversial. Data to guide recommendations for treatment are inconclusive or conflicting. Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke. Until more definitive data are available, it is generally agreed that a cautious approach to the treatment of arterial hypertension should be recommended. Subjects who have other medical indications for aggressive treatment of blood pressure should be treated.

In subjects who received IV tPA blood pressure should be managed according to post IV tPA management protocols (systolic blood pressure is <185 mm Hg and their diastolic blood pressure is <105 mm Hg) within the first 24 hours.

In subjects who are reperfused after mechanical embolectomy (defined as achieving TICI 2b or TICI 3) systolic blood pressure should be maintained at 140 mm Hg in the first 24 hours to minimize the risk of reperfusion related ICH. In subjects who do not achieve recanalization after thrombectomy similar B/P management orders should be applied as for the control subjects within each center.

Some centers use induced hypertension in patients with occlusive disease and in these centers, management of subjects should occur per local guidelines and protocols. In exceptional cases, a physician may prescribe vasopressors to improve cerebral blood flow. If drug induced hypertension is used, close neurological and cardiac monitoring is recommended.

Because arterial blood pressure is a dynamic parameter, it is important to monitor it frequently, especially during the first day of stroke, to identify trends and extreme fluctuations that would require intervention. If/when lowering the blood pressure is indicated, it should be done in a well-controlled manner.

7.7.2 Glucose management

Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in subjects with acute ischemic stroke.

7.8 Day 5-7 / Discharge

The subject may be discharged from the hospital when clinically stable, at the Investigator's discretion. The following data will be collected between Day 5-7 (if subject remains in the hospital) or prior to discharge, whichever is earlier:

- In hospital medical management details
- NIHSS
- mRS (blinded assessor)
- Repeat imaging - MRI T2 Flair is not required but may be performed to re-assess final core infarct volume, at the treating physician's discretion, per local practice. CT may be performed if MRI is contra-indicated. If performed, this imaging will be collected and reviewed by the Core Lab.
- Adverse events and any treatment administered
- Subject disposition

For all subjects who remain in hospital after the Day 5-7 assessments, adverse events and any treatment administered will also be recorded through Discharge. For all subjects who expire prior to the Day 5-7/Discharge assessment, available information regarding the primary cause of death and date/time of death will be recorded, as well as whether the subject was made "do not resuscitate" (DNR) or "comfort care only" prior to expiration.

Deaths MUST be reported to Stryker NV within 24 hours of becoming aware, preferably by CRF completion. In the event that the EDC system is unavailable a written report by e-mail or fax is acceptable.

7.9 Post Discharge Follow-up

The designated staff at the clinical site will review the study requirements with the subject to maximize compliance with the follow-up schedule. The staff will instruct subjects to return for

follow-up assessments according to the study Time and Events Schedule in Table 5. Study staff should establish a date for the follow-up visits with the subject and if possible, schedule the visits at the time of hospital discharge.

The study will be considered complete (with regard to the primary endpoint) after all subjects have completed Day 90 (± 14) follow-up assessments. Requirements of each follow-up evaluation are detailed below.

7.9.1 Day 30 (± 14)

At Day 30 (± 14) the following study assessments should be performed via an in person visit:

- NIHSS
- mRS (by blinded assessor) - If subject is unable to return to the clinic for the Day 30 ± 14 visit, a telephone mRS assessment is preferable to no assessment
- Adverse events and any treatment administered

For all subjects who expire prior to the Day 30 assessment, available information regarding the primary cause of death and date/time of death will be recorded, as well as whether the subject was made "do not resuscitate" (DNR) or "comfort care only" prior to expiration.

Deaths MUST be reported to Stryker NV within 24 hours of becoming aware, preferably by CRF completion. In the event that the EDC system is unavailable a written report by e-mail or fax is acceptable.

7.9.2 Day 90 (± 14)

At Day 90 (± 14) the following study assessments should be performed via an in person visit:

- NIHSS
- mRS (by blinded assessor) - If subject is unable to return to the clinic for the Day 90 ± 14 visit, a telephone mRS assessment is preferable to no assessment
- Adverse events and any treatment administered

For all subjects who expire prior to the Day 90 assessment, available information regarding the primary cause of death and date/time of death will be recorded, as well as whether the subject was made "do not resuscitate" (DNR) or "comfort care only" prior to expiration.

Deaths MUST be reported to Stryker NV within 24 hours of becoming aware, preferably by CRF completion. In the event that the EDC system is unavailable a written report by e-mail or fax is acceptable.

8 Statistical Methods

8.1 Sample Size Estimate and Justification

The adaptive sample size was judged through simulations based on the following assumptions:

The maximum trial size is 500 subjects, randomized equally between the two arms. Because of the adaptive nature of the design, the actual sample size may be less, with the minimum being 150 subjects.

We investigated treatment effects that increased the expected weight by 0, 0.5, 0.75, 1.0, 1.25, and 1.5 units above control for all infarct sizes. The effect size of 0.5 units of weight is small, and consequently a trial of this size is unlikely to detect it, the trial offers roughly 30% power in scenarios with this effect size. The effect sizes of 1.25 and 1.5, on the other hand, are very large and the trial offers better than 95% power to detect such improvements. The design provides 86% power to detect an effect size of 1 unit. The Type I error probability is controlled to be no more than 2.5%.

Expected sample sizes are smallest when the treatment effect is very small (when early stopping for futility is likely) and when the treatment effect is very large (when early stopping for expected success is likely). The trial enrolls more subjects when the data are inconclusive about whether the device has a substantial positive effect.

The distribution of mRS outcomes for the control arm in the simulations was based on combined data from the following study sub-populations: IMS III IV tPA arm (N=222)[58]; MR RESCUE penumbral pattern with IV tPA arm (N=34) [59]; PROACT II heparin arm (N=59) [25]; MELT no treatment arm (N=57) [26]; DEFUSE 2 Target Mismatch without reperfusion arm (N=32) [90]; Merci Registry non-revascularized, non-intubated, treated ≥ 6 hours (N=30) [Sponsor-derived from raw dataset]; Natural History of MCA and ICA occlusions (N=40) [22]; and SENTIS no treatment arm (N=106) [101]. The distribution of the mRS outcomes for the control arm used in the simulations is shown in Table 6**.**

Table 6. Distribution of mRS outcomes for the control arm in the simulations

mRS	0	1	2	3	4	5	6
Proportion	0.07	0.13	0.12	0.17	0.20	0.11	0.19

8.2 Control of Systematic Error/Bias

In order to control systematic error/bias, the randomization will be take place using either the use of an independent IVRS or web based system or through pre-printed, block randomization envelopes prepared by a qualified and independent biostatistician.

In order to protect the status of the blind and minimize potential bias, an independent statistician who is not involved with the conduct of the study will perform the interim analyses for the primary endpoint.

The design mitigates potential bias due to the enrichment by preventing early stopping for expected success immediately following an enrichment decision. We require an additional 100 subjects to be enrolled in the enriched population before making a decision to stop enrollment.

8.3 Eligibility of Subjects, Exclusions, and Missing Data

Based on previous experiences in clinical trials of acute stroke, minimal loss to follow-up (LTFU) is expected for the 90-day assessment of the primary outcome measure. In the MERCI study, 7.2% (11/151) of subjects were LTFU, in Multi MERCI 2.4% (4/164) were LTFU, and in the TREVO 2 study, 3.4% (6/178) were LTFU. All efforts should be made to ensure near complete follow-up, with particular focus on the assessment of primary outcome (mRS at 90 days) and mortality.

Nevertheless, some missing data may still occur. All randomized subjects will be included in the primary endpoint analysis (ITT). In case of missing 90-day mRS values, the 30-day mRS values will be incorporated into the imputation model. Refer to the adaptive design plan for details in **Appendix F**.

8.4 Population Definitions

Screened: Includes any subject who is considered for participation for the trial, whether or not they sign an informed consent.

Screen-failed: Includes any subject who is considered for participation for the trial, who either fail to meet one or more of the inclusion criteria or who meet one or more of the exclusion criteria; subjects can be screen failed based on general inclusion/exclusion criteria, or imaging inclusion/exclusion criteria (these subjects may or may not have signed an informed consent).

Enrolled: Includes any subject who has been randomized based upon the results of the post-processing of the baseline MRI-DWI or CTP-rCBF baseline images, and Clinical Imaging Mismatch profile (informed consent must be obtained prior to randomization).

Completed: Includes any subject who is enrolled/randomized and completes the study follow up at Day 90 (± 14), or is known to have expired before 90 days post randomization.

Discontinued: Includes any subject who is enrolled/randomized but who fails to complete the study follow up at Day 90 (± 14), and who has not expired before 90 days post randomization.

Wake-up Strokes: Subjects known to have symptoms first detected on awakening from sleep.

Witnessed Strokes: Subjects with last known well time and symptoms first observed time known to be the same.

Un-witnessed Strokes: Subjects with last known well time and symptoms first observed time known to be different, but not known to have symptoms first detected on awakening from sleep.

8.5 Analysis Populations

Intent-to-Treat (ITT): Includes all enrolled/randomized subjects. This includes all subjects randomized to receive the Trevo device (even if they never receive it or receive treatment with another device), and all subjects randomized to the control arm (regardless of actual treatment received). Final analysis is only on the enriched population (refer to adaptive design plan in **Appendix F**). This population is the primary population for all efficacy parameters.

Modified ITT (mITT): The same as the ITT population except subjects are analyzed based upon actual treatment received. Subjects who receive only medical therapy are included in the control arm, and subjects who receive any device-based therapy are included in the Trevo arm.

Per-Protocol (PP): A subset of the intent-to-treat population, including subjects who did not violate the inclusion/exclusion criteria or experience significant protocol deviations.

8.6 Interim Analysis

Primary endpoint interim analyses will begin after 150 subjects have been enrolled, and subsequent interim analyses will take place after every 50 subjects.

The analysis performed at each interim analysis will include:

- Modeling of the treatment effect for each infarct size in the population,
- Longitudinal modeling to impute final outcomes for subjects for which we have 30-day mRS scores but not 90-day mRS scores, and
- Estimation of the distribution of infarct sizes.

The mathematical details and assumptions for these analyses are described in **Appendix F**.

The possible decisions that may be made at the interims are to:

- Stop the trial early for futility,
- Enrich the population if it appears that the device benefits one subset of the population considerably more than another, or
- Stop enrollment for expected success.

Each decision is based on the predictive probability that the trial would be a success if subjects were enrolled to the end of the trial. The rules for each decision are defined below. Additional details pertaining to statistical models are given in the adaptive design plan in **Appendix F**.

8.6.1 Interim Monitoring for Early Futility

Interim safety analyses will be performed concurrently with the primary endpoint analyses.

The trial stops for futility if there is less than 10% predictive probability that the trial would be successful if enrolled to the maximum sample size under any enrichment possibility.

8.6.2 Enrichment

Enrichment decisions can occur starting at 150 subjects enrolled and the last opportunity to enrich is at 400 subjects. The candidate enriched populations that the trial considers are based on infarct sizes. The five possible subpopulations are defined by infarct size as measured using MR-DWI or CTP-rCBF maps:

1. The full population of infarct sizes 0 to 50 cc
2. Infarct sizes of 0 to 45 cc
3. Infarct sizes of 0 to 40 cc
4. Infarct sizes of 0 to 35 cc
5. Infarct sizes of 0 to 30 cc

If the population is enriched, subjects with larger infarct sizes are no longer enrolled, and the final efficacy analysis omits subjects with larger infarct sizes from consideration. Enrichment decisions are irreversible, but the trial can enrich the population further after it has already been enriched.

The design will enrich if one of the following conditions is met:

If the highest currently open group of five (5) infarct sizes has less than 40% posterior probability of an average positive treatment effect, then this group of infarct sizes will no longer be enrolled in the trial. This rule is applied before the second enrichment rule, and may only be applied once per interim analysis.

If the predictive probability of a positive trial increases by at least 10% by enriching to a smaller subpopulation, then the trial will enrich to the smallest subpopulation that satisfies this criterion.

8.6.3 Interim Monitoring for Expected Success

The trial may only stop enrollment for expected success if at least 100 subjects have been enrolled since the last enrichment. The decision is based on the predictive probability of

trial success for both the weighted mRS analysis and dichotomous mRS analysis, and if no further subjects are enrolled. The threshold for this predictive probability is 95% for the 200 and 250 subject interim analyses, 90% for the 300 and 350 subject interim analyses, 85% for the 400 subject interim analysis, and 80% for the 450 and 500 subject analyses. If the predictive probability exceeds the threshold at an interim analysis, then enrollment stops for expected success.

All subjects will be followed through their 90 day assessment and the final analysis for trial success will be based on the full data through 90 days.

8.6.4 Longitudinal Model

At the time of each interim analysis, some subjects may not have completed the 90-day follow-up period for mRS. Because subjects will also be evaluated for mRS at 30 days these scores will be used to assist in making decisions at the interims. We estimate the probability distribution of 90-day mRS conditional on 30-day mRS and use this estimated distribution to inform a longitudinal model for imputing final mRS outcomes for subjects with known 30-day mRS but unknown 90-day mRS.

8.7 Statistical Analysis

The final weighted and dichotomous analyses will be performed only on the enriched population, and assumes a constant treatment effect over all infarct sizes that are in the population at the end of the trial.

The trial is considered successful if there is sufficiently high posterior probability that the treatment effect is positive. The threshold for success is adjusted to account for the degree to which the population has been enriched, and depends on the following factors:

- The number of enrolled subjects in the enriched population at the time of the enrichment decision (N_1)
- The number of enrolled subjects outside the enriched population (N_2)
- The number of subjects enrolled after the enrichment decision (N_3).

Specifically, the threshold is calculated as:

$$\Phi(\sqrt{1+\frac{N_2}{N_1+N_3}}\Phi^{-1}(p_{crit})),$$

where Φ is the standard normal cumulative distribution and $p_{crit} = 0.986$ is a critical probability evaluated via simulation to control Type I error probability. If no enrichments are made during the trial, then the success threshold is equal to p_{crit}, and the threshold increases as enrichment becomes earlier and more aggressive.

The primary analysis of mRS scores for the interim and final analyses will be performed by Berry Consultants, LLC using custom code developed in Java and R software.

The Secondary efficacy and safety analyses will be performed by Stryker NV Biostatistics personnel using SAS, version 9.2 or higher. Pooling of data across institutions and stratification will be described in the Statistical Analysis Plan.

8.7.1 Baseline Comparability

Baseline comparability between the two arms will be done using descriptive statistics and will be described in detail within the Statistical Analysis Plan.

8.7.2 Pooling Across Institutions

Results for the primary efficacy endpoint will be presented by site and treatment group. Poolability across institutions will be assessed using an ANCOVA on the weighted mRS with terms for treatment group, site, and the interaction of treatment group and site. A p-value less than 0.10 for the interaction term will be taken as evidence that there are significant differences in treatment effect between sites. If the effect is found to vary by site, then the effect will be analyzed using a hierarchical model with random site effect.

8.7.3 Other Pre-planned Analyses

Both Arms:

1. Incidence of symptomatic ICH (per the SITS MOST definition)

Treatment Arm only:

2. Frequency of functional independence (mRS 0-2) by reperfusion status post-device and post-procedure

8.7.4 Health Economics Information

Sites will be asked to collect hospital billing and resource utilization information for all randomized subjects. The UB-04 form will be collected within the United States while in other countries a CRF containing similar information will be completed. This information may be used for future analyses to compare overall health care costs and resource utilization between mechanical intervention and standard medical care.

9 Data Management

9.1 Data Collection and Processing

Subject data will be collected in a secure electronic data capture (EDC) system via the Internet. All pertinent data will be entered by the study site personnel into the electronic Case Report Forms (CRFs). A unique subject ID number will be assigned to each subject. Every reasonable effort should be made to complete data entry within one week of data collection. Any data discrepancies may be queried during ongoing review of data by Stryker NV or may be identified and queried during routine monitoring visits. Data monitoring will be performed to verify data accuracy and ensure queries are resolved. The Principal Investigator or Sub-investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate CRFs. Changes to data previously submitted to the sponsor will require a new electronic signature by the investigator to acknowledge/approve the changes.

Results from Core Labs and CEC reviews will also be entered into the EDC system and will be electronically signed by the reviewer responsible for entering this data. Ongoing data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to Core Labs or Clinical Events Committee for appropriate resolution.

10 Monitoring Procedures

Monitoring visits to the clinical sites will be made periodically during the study, to ensure that all aspects of the current, approved protocol/amendment(s) are followed. Original source documents will be reviewed for verification of data in the electronic database. The Investigator/institution must allow direct access to original source documents by Stryker NV personnel, its designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

It is important that the Investigator and/or relevant study site personnel are available during the monitoring visits and that sufficient time is devoted to the process. In order to perform her or his role well, the monitor must be given access to primary subject medical records, which support the data that has been entered into the study CRFs. Access to Protected Health Information (PHI) by the study monitor will be disclosed to the subject within the Informed Consent Form. See ICF template provided in **Appendix D**.

10.1 Auditing

The study may be subject to a quality assurance audit by Stryker NV or a designee, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and

relevant study personnel are available during any audits and that sufficient time is devoted to the process.

10.2 Investigational Device Accountability

Investigational device accountability records must be maintained at the study site. The quantity of devices received by the study site, those returned to Stryker NV, and those devices used at the study site will be recorded in the device accountability log. The Investigator must explain in writing the reasons for any discrepancies noted in device accountability log. Investigational devices will be shipped to sites after all essential documents are collected, the Site Initiation Visit and training of all required study personnel is completed, and the site is approved to enroll. In some circumstances, at the discretion of the Project Manager, the investigational devices may be shipped to coincide with the Site Initiation Visit, if a site is anticipated to complete all requirements to be eligible to begin enrollment during the visit.

11 Adverse Events

11.1 Adverse Event Definitions and Classification

Term	Definition	Reference
Adverse Event (AE)	Any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation.	ISO 14155-1
Adverse Device Effect (ADE)	Any untoward and unintended response to a medical device. *Note 1*: This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. *Note 2*: This definition includes any event that is a result of a user error.	ISO 14155-1

Term	Definition	Reference
Serious adverse event (SAE)	An adverse event that: • led to death • resulted in a life-threatening illness or injury • resulted in a permanent impairment of a body structure or a body function • required inpatient hospitalization or prolongation of existing hospitalization • resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function • led to fetal distress, fetal death or a congenital abnormality or birth defect	ISO 14155-1
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or if circumstances had been less fortunate.	ISO 14155-1
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.	21 CFR Part 812

Underlying (pre-existing) symptoms or diseases are not reported as Adverse Events (AEs) unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an adverse event, but should only be reflected as an outcome to another specific AE. Any AE experienced by the study subject after enrollment (equal to the time of randomization) must be recorded in the CRF.

All AEs and SAEs will be monitored and collected from the time of enrollment (equal to the time of randomization) through 90 day follow-up visit. All SAEs and UADEs must be reported to Stryker NV within 24 hours of becoming aware of their occurrence in order to comply with Stryker NV's regulatory reporting requirements.

In subjects who are randomized to the Treatment Arm, the Investigator must assess the relationship of the adverse event to the study device using the following criteria categories and definitions:

Unrelated - The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.

Possible - The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to the investigational product.

Probable - There is a strong relationship to the investigational product, or recurs on re-challenge, and another etiology is unlikely.

Highly Probable - There is no other reasonable medical explanation for the event.

In subjects who are randomized to the Treatment Arm, the Investigator must assess the relationship of the adverse event to the index procedure using the following categories and definitions:

Unrelated - The adverse event is determined to be due to a concurrent illness or effect of a device/drug and is not related to the index procedure.

Possible - The adverse event is determined to be potentially related to the index procedure, and an alternative etiology is equally or less likely compared to the potential relationship to the index procedure.

Probable - There is a strong relationship to the index procedure, or recurs on re-challenge, and another etiology is unlikely.

Highly Probable - There is no other reasonable medical explanation for the event.

11.2 Adverse Events Reporting Requirements

All AEs will be recorded in the appropriate CRFs.

All SAEs and UADEs shall be reported within 24 hours of becoming aware to Stryker Neurovascular via data entry into the CRFs. All procedure or device-related deaths shall be reported to the IRB/EC no later than 24-48 hours of becoming aware or per the IRB/EC reporting requirements. If access to CRFs is not available then the information can be faxed to the Stryker Neurovascular Safety Department personnel listed in current Study Contacts List provided in the Study binder.

The site Principal Investigator is responsible for informing the IRB/EC of UADE, SAE, and/or Adverse Events as required by local procedure. A copy of this report should be provided to Stryker NV.

11.3 Device Failures, Malfunctions, and Product Nonconformities

All Trevo device failures, malfunctions, and product nonconformities will be documented on the appropriate CRF and the involved device(s) should be returned to Stryker NV for analysis, if possible. Instructions for returning the investigational device(s) will be provided to the study sites in their Study binder. Device failures and malfunctions should also be documented in the subject's medical record.

All Trevo device failures, malfunctions, and product nonconformities shall be reported within 24 hours of becoming aware to Stryker Neurovascular via data entry into the CRFs. If access to the EDC system is not available then the information can be faxed to the Stryker Neurovascular Safety Department personnel listed in the current Study Contacts List provided in the Study binder.

NOTE: Trevo device failures, malfunctions, and product nonconformities should be reported as soon as possible after becoming aware of them, on the appropriate CRF, and should not to be reported as adverse events (in and of themselves). However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate CRF.

All Stryker Neurovascular nonstudy device malfunctions and nonconformities related to ancillary devices used in the procedure should be reported to the local Stryker customer service center.

11.4 Reporting to Regulatory Authorities / IRBs / ECs / Investigators

Stryker NV is responsible for the coding and reporting of all verbatim adverse events to all participating investigators and regulatory authorities, as applicable. Stryker NV will utilize the MedDRA (Medical Dictionary for Regulatory Affairs) to code all AEs reported in the trial. UADEs will be reported to FDA by Stryker NV as per 21 CFR 803.

The Site Principal Investigator is responsible for informing the IRB/ Ethics Committee (EC) of UADE, SAE, and/or as required by local procedures. A copy of this report should be sent to the Stryker NV Clinical Research Associate. Refer to **Section 13.2.1** for information pertaining to the Clinical Events Committee (CEC).

Stryker NV will identify sites at which adverse events (AEs) and protocol deviations occur in annual reports and correspondence with the FDA.

For Canadian sites, Health Canada Mandatory Problem Reporting requirements as stated in the Medical Device Regulations must be followed:

The manufacturer and importer of a medical device are required to report any event that is:

- Related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in its direction for use

- Has led to death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur

A preliminary report is required within 10 days of the manufacturer or importer becoming aware of the incident if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person or within 30 days if it has not led to a death or serious deterioration but could do so were it to recur.

For German sites, the process for reporting SAEs as documented in "Procedure Regarding SAE Reporting: In line with Directive 93/42/EEC as amended – Annex X – Section 2.3.5" and according to § 3 (6) of the Ordinance on Medical Devices Vigilance will be followed. Generally:

- SAEs occurring in Germany must be reported to BfArM immediately if a causal relationship between the SAE and the investigational medical device cannot be excluded.

- An overall assessment of all SAEs must be reported to BfArM quarterly.

Additionally, Stryker NV must report all SAEs occurring in Germany to the competent authorities of other contractual states of the Agreement on the European Economic Area immediately if the clinical trial is also performed in those countries.

12 Risk Benefit Analysis

It is possible that subjects enrolled into this trial will receive no direct benefit from participation. There may be additional risks to subjects randomized to the Trevo thrombectomy plus medical management arm in addition to those that are currently known or anticipated for patients treated within 6 hours from symptom onset or time last seen well. See **Section 12.3**.

All subjects screened for the trial will undergo MR or CT multi-modal diagnostic imaging to assess for hemorrhage, to verify occlusion location, and to measure the core infarct volume. Risks associated with the baseline imaging conducted as part of the trial are as follows in **Sections 12.1 and 12.2**.

Benefits of Trevo thombectomy plus medical management may include higher revascularization rates which in turn are predictive of better clinical outcomes. [17] Potential benefits justify the anticipated risks, given the safeguards in place to monitor patient safety throughout the trial.

12.1 CT/MR Imaging

CT/MR scans of the brain obtained at baseline, 24 (-6/+24) hours post procedure, and sometimes at discharge are considered standard medical care. The risk associated with performing a CT/MR scan is the ionizing radiation exposure. The radiation dose that is received is the same dose that would be received from the clinical care to assess and treat the underlying medical condition. There is no additional risk of increased ionizing radiation exposure as a result of participation in this study.

A small amount of radiation is used to obtain a CT Angiogram (CTA). The radiation dose from this study is below the levels that are thought to result in a significant risk of harmful effect. There is some chance of an allergic reaction to the x-ray contrast (dye) used during the CTA.

During an MRI or MR Angiogram (MRA) no harmful radiation is involved. The MR contrast dye could cause one of the following in rare cases: mild to moderate headaches; coldness in the arm where dye is being injected; infection; nausea; dizziness; changes in heart rate and/or blood pressure; sneezing; dry mouth; or rash.

Due to differences in standards of care between sites, it is possible that some subjects may receive additional follow-up imaging or neurologic examinations other than those required by the protocol. The risks of these neurologic examinations are negligible, and the subject would likely benefit from enhanced care due to these additional tests.

12.2 Investigational procedure (Treatment arm only)

12.2.1 Diagnostic Angiography

Risks associated with angiography have been well documented and are understood by the medical community. The arteriogram itself can cause problems with brain function and it can potentially make the subject's condition worse. Angiography requires the placement of an intra-arterial catheter for the injection of contrast media to image vessels in the brain, and the most common complication is access-site hematoma (4.2%). [102] Other risks related to the diagnostic angiographic procedure are relatively low but may include:

- Infection
- Bleeding
- Hematoma
- Vessel thrombosis
- Dissection
- Distal embolization
- Pseudoaneurysm and arteriovenous fistula formation
- Vessel injury
- Allergy to the contrast material
- Neurological injury

- Death

The risk of bleeding may be increased when diagnostic angiography is performed in individuals who are receiving anticoagulation and/or antiplatelet therapy. Neurological injury associated with these vascular complications may occur. Renal toxicity and idiosyncratic responses to the injected contrast medium including anaphylactic reactions have also been reported.

12.2.2 Trevo Thrombectomy

For any individual subject, participation and randomization to the treatment arm is no guarantee that they will receive a direct benefit. Completion of the study may benefit the subject's community at large through enhanced knowledge about the risks and benefits of these two treatment modalities: Trevo Retriever plus medical management versus medical management alone.

The potential risks associated with the use of the Trevo Retriever include:

- An air bubble introduced into the blood vessels (air embolism)
- Bleeding or bruising in the access site, or where the puncture is made (hematoma)
- Infection at the access site, or sepsis
- Embolization of a fragment, or the entire thrombus, to a previously uninvolved territory (emboli)
- Vessel spasm
- Pain/headache
- New clot formation (thrombosis)
- A blood vessel tear or puncture (dissection or perforation)
- Distal thrombus – embolization of pieces of the original thrombus "downstream" in the same vascular territory as the original thrombus (distal embolization)
- Blood vessel becomes acutely occluded (re-thrombosis/acute occlusion)
- Ischemia (reduced blood flow) in the brain
- Intra-cerebral hemorrhage (bleeding into the brain)
- False aneurysm formation
- Neurological deficits, including a new stroke
- Death

Refer to the sample Instructions for Use (IFU) in **Appendix E** for table of previously observed rates of procedural risks.

Only trained and experienced physicians will use this device within the trial. The investigational device will be used as per the steps listed within the current Instructions for Use.

However, since the time window in which the device will be used within this study is expanded to between 6 - 24 hours after stroke symptom onset or time last seen well,

participation in the study adds a currently unknown level of risk to the subjects who are randomized to the Treatment arm. Some publications have reported increased rates of cerebral edema, intracranial hemorrhage, and mortality in patients treated with revascularization therapy beyond 6 hours. However other publications have not confirmed this finding, and the potential benefits of Trevo thrombectomy include revascularization, and revascularization has been shown to be correlated with improved clinical outcomes and reduced mortality, [17] therefore potential benefits outweigh the anticipated risks.

12.3 Risk Minimization

Each site must obtain IRB or EC approval prior to screening and enrolling subjects. Every subject or Authorized Legal Representative (LAR) will be required to provide signed Informed Consent prior to participation which will explain their treatment choices and the risks and benefits of being in the study. Finally, several independent committees and core labs will assist in oversight of the study which ensures that any risks to subjects will be minimized.

MRI-DWI or CTP-rCBF neurological imaging maps will be used to measure the core infarct volume and only those subjects who have small to moderate core infarct volumes will be considered for randomization into the trial.

Additionally, risk will be mitigated in the Trevo thrombectomy plus medical management arm by implementation of an adaptive trial design which allows for early and frequent assessment of efficacy and safety parameters in the two study arms, to ensure that the number of subjects exposed to a potentially non-beneficial treatment is minimized.

Safety monitoring of the data, consisting of individual event and aggregate data review, will be ongoing and conducted at a rate commensurate with subject enrollment in the trial.

The DMC will provide subject safety oversight and make recommendations to Stryker NV regarding continuing enrollment, modifying, or stopping the study early based upon a review of the comparative rates of SICH, neurological worsening, stroke-related mortality and all other site-reported SAEs. They will take into account in their decision making and recommendations the rates of procedure-related and device-related events in the treatment arm.

13 Study Committees and Core Labs

13.1 Steering Committee

A Steering Committee has been convened. Responsibilities include oversight of the overall conduct of the study with regard to protocol review and development, study progress, ensuring adequate subject safety oversight, and overall data quality and integrity. The Steering Committee will oversee dissemination of study results through appropriate scientific sessions and publications. The Steering Committee may select additional investigators, based on enrollment and adherence to the protocol, to participate on a Publication Committee. The

Publication Committee will participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

13.2 Safety Monitoring Committees

To promote early detection of safety issues routine medical monitoring will be conducted on an ongoing basis. In addition, the CEC and DMC charters will provide for evaluation of safety events at routine intervals. Process flow, supporting documents, and software programming will allow for 21 CFR Part 11 compliant electronic database access, to CEC members for real time case review and event adjudication.

The CEC and DMC may be un-blinded due to the fact one study group receives an intervention while the second study group does not. The dataset will contain obvious AEs/SAEs specific to the interventional procedure that will, simply by their presence, un-blind those individuals reviewing the data. The DMC procedures are described in more detail in the DMC Charter.

This process requires the dynamic collection of unmonitored data as soon as an event is reported. This is expedited by designated Stryker NV Safety personnel, who are responsible for reviewing safety data within the trial on an ongoing basis, and coordinating the collection of information for inclusion within the CEC event dossier from the sites and Core Labs.

During regularly scheduled monitoring visits, the clinical research monitors will support the dynamic reporting process through their review of source document information.

13.2.1 Clinical Events Committee (CEC)

The CEC will include specialists in stroke neurology and/or neuro-intervention as well as other experts with the necessary therapeutic and subject matter expertise who are not participating in the trial and have no affiliation with Stryker NV. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter. The CEC will be responsible to review and adjudicate the following protocol-defined safety outcome measures and relevant adverse events reported by study investigators. Relevant information and source documents will be provided to assist with their review and adjudication of events.

- Vessel perforation
- Intramural Arterial dissection
- Symptomatic ICH
- Embolization to a new territory
- Neurological worsening (associated with a 4 or more point increase in NIHSS) or possible or confirmed evolution/progression of the index stroke
- All deaths

In cases where their expertise is required the CEC will be asked for an opinion on the following events. However, the Stryker NV safety department will be responsible for their initial review and coding and they will not automatically be sent to the CEC for adjudication:

- *In vivo* device failure (*in vivo* breakage)
- Access site complication requiring surgical repair or blood transfusion
- Other confirmed or suspected Procedure and/or Device-related SAEs with an outcome other than death occurring at any time during subject participation

13.2.2 Data Monitoring Committee (DMC)

The DMC will include specialists in stroke neurology and/or neuro-intervention as well as biostatistics, who are not participating in the trial and have no affiliation with Stryker NV. The DMC is responsible for monitoring subject safety through pre-defined, periodic review of the clinical study safety data. DMC responsibilities, qualifications, membership, meeting frequencies, and procedures are outlined in the DMC charter.

The DMC's role is to monitor and advocate for subject safety throughout the lifecycle of the trial and they will review all SAEs and mortality between both arms, as well as standard tables (as outlined within the DMC charter) at regularly scheduled meetings, and at ad hoc meetings if requested by the Safety Monitor. To ensure the safety of the study and its participants, enrollment for the trial will be held within 24-48 hours of sponsor awareness of 5 consecutively enrolled patient mortalities occurring in either arm. The DMC will be convened within that time interval to review the mortality data and provide its recommendation of study termination, modification, or continuance without modification. Special attention will be given for review of peri-procedural mortality in the treatment arm. If the DMC does not convene within that time interval, then patient enrollment will be automatically suspended. In addition, measurements of safety and effectiveness are integrated within the weighted mRS primary endpoint analysis. The stopping rule for this trial is equivalent to the threshold set for early stopping for futility at the scheduled interim analyses of the primary endpoint, as described within the Adaptive Design Plan (ADP) in **Appendix F**. The DMC assessment of benefit versus harm will take into account both the 90 day dichotomous mRS as well as the average utility weighted mRS at 90 days between the two arms, and the thresholds for early stopping for futility, or success, as described within the ADP.

The DMC will weigh the risk/benefit of continuing the study and will report to the Sponsor, who remains blinded to the raw endpoint analysis data, to continue the study as is, modify the study enrollment population (based on the pre-specified allowed enrichment possibilities), or stop the study because a threshold for futile, or success, has been met. In addition, the DMC may make a recommendation to the Sponsor to stop the study at any time because of non pre-specified ethical or safety concerns, e.g. one group is experiencing a specific harm at a rate that is deemed ethically unacceptable.

During the course of the trial, the DMC will review accumulating safety data to monitor the incidence of Adverse Events and other trends that would warrant modification or termination of the trial. The DMC will meet at pre-specified intervals to assess the data against the pre-specified safety and efficacy stopping rule as described within the ADP in **Appendix F**, and review the safety outcomes in both arms to ensure that the risks do not exceed the benefits. In addition to the pre-specified meetings, the DMC will meet for any other safety concerns that might arise during the active enrollment phase of the trial. In addition, a designated member of the DMC will be sent SAE data at regular time intervals, independent from the pre-planned DMC meeting schedule.

Data will be supplied to, and reviewed by, the DMC as tables and/or listings. After review of the aggregate data, the DMC may request additional information. The DMC can also consider external data when appropriate, (e.g. published articles). Any DMC recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to Stryker NV for consideration and final decision. However, if the DMC at any time determines that a potential serious risk exists to subjects in this trial, the DMC chairman will immediately notify Stryker NV.

An added essential responsibility/function of the DMC is the monitoring and implementing the adaptive design aspects of the trial. The DMC will include a specialist in adaptive design and biostatistics and will be completely independent of the sponsor (Stryker NV). The DMC charter will specify all operating procedures. The DMC will be charged with analyzing the accruing data and implementing the prospectively defined design, as specified within the Adaptive Design Plan. The DMC will report the results of the analysis to Stryker NV.

13.3 Imaging Core Labs

The independent angiographic core lab will review angiographic images from the procedure to determine revascularization and clot location.

The independent CT/MR core lab will review CT/MR images obtained at baseline and at 24 (-6/+24) hours post randomization to determine vessel patency, hemorrhage, and extent of infarcts.

Centralized imaging core labs will be used in this study to provide consistent, independent evaluation of images for confirmation of inclusion criteria. Sites will be provided with instructions for how images should be collected and submitted to Stryker NV within 2 weeks of acquisition of the final required imaging time point at 24 (-6/+24) hours after the procedure. If this timeline cannot be met for any reason, the site should communicate this delay to Stryker NV so that the pending images can be tracked until received.

Ideally MR imaging will be used whenever possible to screen subjects for inclusion into the trial. However, if MR imaging is contraindicated or is unavailable then CT based imaging may be utilized.

Ideally the same imaging modality used at baseline will be used at 24 (-6/+24) hours post randomization. However, for subjects with compromised renal function who had a CT/CTA at baseline, but in whom the treating physician wishes to avoid an additional load of contrast, an MRI/time-of-flight MRA of the intracranial arteries may be obtained instead.

An imaging core lab charter will ensure that consistent policies and procedures are applied throughout the imaging core lab review and determination process. Stryker NV is responsible for tracking images received, requesting required imaging from the sites, performing basic verification of the images received, archiving all images, transmitting and tracking images sent to the core labs, and forwarding the applicable results to the CEC.

13.3.1 Angiographic Core Lab

For each enrolled subject, angiograms must be appropriately de-identified, and sent to the imaging core lab for evaluation. It is important that the images be saved in native DICOM format, and that all imaging sequences are sent (without pre-selecting specific frames). It is also important that the imaging sequences are captured chronologically and are clearly labeled with date and time stamps so that they can be correlated to pre-procedure, post-retriever, and post-procedure time points. Specific imaging transmittal instructions will be provided to the sites by Stryker NV and/or the imaging core lab.

The Angiographic Core Lab will provide an independent assessment of all angiographic inclusion criteria, as well as the secondary efficacy endpoint of modified TICI reperfusion scores post device and post procedure. Additional angiographic scales of interest will also be assessed, including but not limited to AOL, TIMI, and Collateral Flow grade. Refer to **Appendix C** for a description of the scales to be assessed by the Angiographic Core Lab, and the scoring systems that will be used.

13.3.2 CT/MR Core Lab

Baseline and 24 (-6/+24) hour multi-modal CT or MRI imaging will be collected and submitted to the CT/MR Core lab to assess for vessel patency, hemorrhage, and core infarct volume. Vessel patency will be assessed in the Intra cranial ICA; MCA M1 (proximal to striates & distal to striates); MCA M2 (inferior/superior branches); ACA A1; Basilar (proximal, mid, distal segments); and P1 at baseline and at 24 (-6/+24 hours) using CTA/MRA according to the following scale:

0 - occluded
1 - partial patency
2 - patent
N/A - not available or able to assess (based on available imaging)

Hemorrhages will be assessed by CT or MRI and will be categorized according to the ECASS III definitions [103] and/or as RIH, IVH, Subdural, Epidural, or SAH. See Table 7.

Core infact volume will be measured by MR-DWI or CTP-rCBF maps at baseline, and by MRI T2 Flair or CT at later time points.

Table 7. Intracranial Hemorrhage Types

HI-1	Small petechiae within ischemic field without mass effect
HI-2	Confluent petechiae within ischemic field without mass effect
PH-1	Hematoma within ischemic field with some mild space-occupying effect but involving ≤ 30% of the infarcted area
PH-2	Hematoma within ischemic field with space-occupying effect involving > 30% of the infarcted area
RIH	Any intraparenchymal hemorrhage remote from the ischemic field
IVH	Intraventricular hemorrhage
Subdural	Blood between the dura mater and the arachnoid mater
Epidural	Blood between the dura mater and the skull
SAH	Subarachnoid hemorrhage

14 Ethical Considerations

14.1 Compliance with Good Clinical Practices (GCP)

The Investigator will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory (local) requirements; whichever affords the greater protection to the subject.

14.2 Institutional Review Board/ Ethics Committee

A copy of the protocol, proposed Informed Consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/EC for written approval. A copy of the written IRB/EC approval of the protocol and Informed Consent form must be received by Stryker NV before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator must notify the IRB/EC of deviations from the SAEs/UADEs occurring at the site and other SAE/UADE reports received from Stryker NV in accordance with local IRB/EC procedures and regulations.

The Investigator is responsible for obtaining annual IRB/EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Stryker NV.

14.3 Written Informed Consent Form

Stryker NV will provide a sample Informed Consent Form (ICF) to the Investigator to prepare for use at his/her site, attached as **Appendix D**. The ICF documents should be translated into the language(s) understandable to potential subject population(s).

Stryker NV and the reviewing IRB/IEC must approve the ICF before use at that site. The ICF must be in agreement with current Good Clinical Practices (GCP) guidelines, the Declaration of Helsinki, and the International Conference on Harmonization (ICH).

Before participating in the clinical trial, each subject or his/her legally authorized representative (LAR) must give written Informed Consent after the context of the study has been fully explained in a language that is easily understood by the subject or LAR. The subject or LAR must also be given the opportunity to ask questions and have those questions answered to his/her satisfaction.

Written Informed Consent must be recorded appropriately by means of the subject's, or LAR's dated signature. The consent process must be documented in the subject's medical chart. At U.S. sites, electronic informed consent may be utilized in accordance with FDA's Guidance on the Use of Electronic Informed Consent in Clinical Investigations if approved by the site's IRB.

Note - If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if, the subject or the representative or person of trust is not available to sign. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research. (Not applicable to US. Sites.)

14.4 Amending the Protocol

This protocol must be followed exactly. It can be altered only by written amendments made by Stryker NV. Following appropriate approval by Stryker NV, the amended protocol will be submitted to the required regulatory agencies before being distributed to all participating sites. Each site must obtain IRB/EC approval before implementing the revised protocol.

14.5 Protocol Adherence

Prior to beginning the study, the Investigator must sign the Investigator Agreement and Signature page documenting his/her agreement to conduct the study in accordance with the protocol. An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Each deviation from the protocol must be documented with the date and reason for the deviation and reported to Stryker NV as soon as possible, and to the IRB/EC per local guidelines and government regulations. Major and minor protocol deviations are defined within **Appendix B**.

15 Study Administration

15.1 Pre-Study Documentation Requirements

Prior to enrolling any subjects into the trial the site must complete all pre-study essential documents, and these must be confirmed to be on file with Stryker NV:

- Site PI's CV and current medical license
- An operator qualification form (statement of experience) for at least one operator
- W-9 (or equivalent in other countries) to facilitate payment
- A fully executed clinical trial agreement
- IRB/EC approval of the study and the Informed Consent Form
- Documentation of all required study training
- Documentation of a completed Site Initiation Visit

No site may begin enrolling subjects until they receive written approval/authorization from Stryker NV.

15.2 Record Retention

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study subjects in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with Stryker NV or in compliance with other regulatory requirements. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. Stryker NV must receive written notification of this custodial change.

15.3 Criteria for Terminating Study

Stryker NV reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators and associated IRB/EC will be notified in writing in the event of termination.

15.4 Criteria for Suspending/Terminating a Study Site

Stryker NV reserves the right to stop the enrollment of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled or if the site has multiple or major protocol violations without justification or fails to follow remedial actions. Notification of termination of a Study Site will be made by Stryker NV to the appropriate regulatory agencies, as required.

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17 Appendices

Appendix A. Abbreviations

Abbreviation	Full Term
ACA	Anterior Cerebral Artery
ADC	Apparent Diffusion Co-efficient
ADP	Adaptive Design Plan
AE	Adverse Event
AHA	American Heart Association
AIS	Acute Ischemic Stroke
AOL	Arterial Occlusive Lesion
ASA	American Stroke Association
AT	As Treated
CA	Competent Authority
CEC	Clinical Events Committee
CIM	Clinical Imaging Mismatch
CRF	Case Report Form
CT	Computerized Tomography
CTA	Computerized Tomography Angiography
CTP	Computerized Tomography Perfusion

Abbreviation	Full Term
DBP	Diastolic Blood Pressure
DE	Distal Embolization
DMC	Data Monitoring Committee
DNR	Do Not Resuscitate
DRSAE	Device-related SAE
DWI	Diffusion Weighted Imaging
EC	Ethics Committee
EE	Efficacy Evaluable
ENT	Embolization to New Territory
ESO	European Stroke Organization
GCP	Good Clinical Practice
HCT	Hematocrit
HI-I	Petechial hemorrhage type I
HI-II	Petechial hemorrhage type II
Hr/Hrs	Hour/Hours
IA	Intra-Arterial
ICA	Internal Carotid Artery

Abbreviation	Full Term
ICA-T	Internal Carotid Artery Terminus
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous
IVH	Intraventricular Hemorrhage
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
LAR	Legally Authorized Representative
LTFU	Lost To Follow Up
LVO	Large Vessel Occlusion
M-1	The initial horizontal segment of the MCA, prior to the first bifurcation or trifurcation
M-2	The portions of the MCA distal to the first bifurcation or trifurcation, but prior to the second bifurcation
MCA	Middle Cerebral Artery

Abbreviation	Full Term
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis in Cerebral Infarction
NIHSS	National Institute of Health Stroke Scale
PH-I	Parenchymal hemorrhage type 1
PH-II	Parenchymal hemorrhage type 2
PP	Per Protocol
PRSAE	Procedure-related SAE
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PWI	Perfusion Weighted Imaging
rCBF	Relative Cerebral Blood Flow
RIH	Remote Intracerebral Hemorrhage
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAH	Subarachnoid Hemorrhage

Abbreviation	Full Term
SBP	Systolic Blood Pressure
SICH	Symptomatic Intracranial Hemorrhage
TICI	Thrombolysis in Cerebral Infarction
TIMI	Thrombolysis in Myocardial Infarction
TLSW	Time Last Seen Well
tPA	Tissue Plasminogen Activator (alteplase)
UADE	Unanticipated Adverse Device Effect
UK	Urokinase
USADE	Unanticipated Serious Adverse Device Effect
WUS	Wake Up Stroke

Appendix B. Definitions

Access Site Complication: Complication related to the vascular access site for the index procedure including but not limited to bleeding, hematoma, pseudoaneurysm, tears, pain or occlusion. Some of these complications may require additional treatment such as blood transfusion or surgical repair.

Adverse Event (AE): Any unintended disease or injury or untoward clinical sign in a research subject. NOTE - This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Device Malfunction/Nonconformity: The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Device-Related Serious Adverse Event (DRSAE): Trevo device related vascular perforation or intramural arterial dissection, symptomatic ICH, embolization to a new territory, intra-procedural death, or device failure (*in vivo* breakage).

Distal Embolization (DE): Any downstream occlusion distal to the target artery lesion (TAL), into the target ischemic territory, is considered DE unless complete angiogram or pre procedure non-invasive imaging demonstrated patency of these distal branches.

Early Response: A NIHSS drop of ≥10 from baseline or an excellent score of NIHSS 0 or 1 at Day 5-7 / Discharge (whichever is earlier).

Embolization to New Territory (ENT): Embolization into a previously uninvolved area of the brain, e.g. ACA embolization during MCA-M1 thrombectomy procedure. In ICA terminus occlusion, any MCA or ACA occlusion post procedure is considered distal embolization (DE) and not ENT. However, if pre procedure patency of these previously uninvolved territories is documented by complete angiogram or pre-intervention non-invasive imaging, then it would be considered ENT.

Epidural hemorrhage: Blood between the dura mater and the arachnoid mater.

Good Clinical Outcome: A measure of neurologic functional outcome with a score of 0–2 on the modified Rankin Scale (mRS), usually assessed 90 days after treatment.

Intracranial hemorrhage: A hemorrhage, or bleeding, within the skull

Intramural arterial dissection: A tear or damage to the inner arterial wall that occurs during the index procedure. The intramural arterial dissection may be identified angiographically as minor radiolucent area to luminal filling defect on imaging.

Intraprocedure Mortality: Death occurring during the index thrombectomy procedure

Intra-ventricular Hemorrhage (IVH): Bleeding into the brain's ventricular system.

***In vivo* (breakage) device failure:** Breakage of the Trevo device in the vasculature during the index procedure.

Medical Management: In broad terms, medical management as the label for the Control arm means no intra-arterial intervention with drugs or devices. Furthermore, after randomization, a subject cannot be placed on intravenous thrombolytic therapy. The specific implementation of best medical management should be consistently applied and in accord with the relevant AHA or ESO guidelines, as applicable in the country of treatment.

Modified Rankin Scale: Scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.

Neurological worsening: A 4 or more point increase in NIHSS from baseline. Neurological worsening could be new or evolution/progression of the index stroke.

NIHSS Score: An assessment to objectively quantify the impairment caused by a stroke. It is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

Parenchymal hemorrhage type 1 (PH-1): A hematoma in $\leq$ 30% of the infarcted area with some slight space-occupying effect.

Parenchymal hemorrhage type 2 (PH-2): Dense hematoma > 30% total of the infarcted area with substantial space-occupying effect or any hemorrhage area outside the infarcted area.

Petechial hemorrhage type I (HI-1): Small petechiae along the margins of the infarct.

Petechial hemorrhage type II (HI-2): More confluent petechiae within the infarcted area but without space-occupying effect

Pre-stroke disability: Obtained at baseline, but representative of the subject's status before the index stroke, assessed by mRS on medical history obtained from subject's medical chart, or family members.

Procedure-Related Serious Adverse Event (PRSAE): Procedure-related events that include, but are not limited to vascular perforation or intramural arterial dissection,

symptomatic ICH, embolization to a new territory, or access site complication requiring surgical repair or blood transfusion, intra-procedural death, or device failure (*in vivo* breakage).

Protocol Deviation: Any alteration/modification to the current IRB/EC-approved protocol. The protocol includes the detailed protocol, protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the research study. Note: Any permanent change to the protocol constitutes an amendment that must be submitted to the Institutional Review Board/Ethics Committee for approval prior to initiation. Deviations may be further classified as:

- Major deviation: a deviation that may impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study, such as but not limited to: enrollment without obtaining appropriate informed consent; violation of inclusion/exclusion criteria; randomization irregularities including treatment arm crossover; confounding procedure by using non allowed therapies; non reporting of SAEs/UADEs and study product non conformities; and protocol required assessments repeatedly not completed at the required time windows

- Minor deviation: a deviation that does not impact subject safety, compromise the integrity of study data and/or affect subject's willingness to participate in the study, such as but not limited to: follow up assessments not conducted or conducted outside of the required time windows.

Protocol Exception: Any single protocol deviation that is approved by Stryker NV prior to its initiation, and documented in writing. Note: Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB/EC for approval prior to initiation.

Remote Intracerebral Hemorrhage (RIH): Any intraparenchymal hemorrhage remote from the ischemic field.

Serious Adverse Device Effect (SADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Serious Adverse Event (SAE): An adverse event in a research subject that led to a death, or led to a serious deterioration in the health of the subject that resulted in a life-threatening illness or injury, or resulted in a permanent impairment of a body structure or a body function, or required in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function. SAEs are a subset of AEs.

- NOTE 1 – This definition does not imply that there is a relationship between the serious adverse event and the device under investigation.

- NOTE 2 – A planned hospitalization/procedure for a pre-existing condition or a condition required by the protocol, without serious deterioration in health is not considered serious but should be recorded as an AE. Deterioration in health as a result of the planned hospitalization/procedure should be recorded as a new AE.

Stroke: An acute neurological event with focal symptoms and signs lasting ≥ 24 hours. Stroke can be sub-classified as Hemorrhagic or Ischemic.

- **Hemorrhagic Stroke:** A symptomatic intracerebral, subarachnoid, or primary intraventricular hemorrhage. To be considered a hemorrhagic stroke, the patient must experience new symptoms (e.g., new severe headache) that last for at least 24 hours (symptoms do not need to be associated with a new neurological deficit).

- **Ischemic Stroke:** A neurological deficit that is thought to have an ischemic cause and is detectable on examination at least 24 hours after onset of symptoms.

Stroke-related Death: Death related to the index stroke; to systemic complications associated with the index stroke, or a new stroke.

Subarachnoid Hemorrhage (SAH): Bleeding into the subarachnoid space - the area between the arachnoid membrane and the pia mater surrounding the brain.

Subdural hemorrhage: Blood between the dura mater and the skull.

Symptomatic ICH (SICH): The primary protocol definition is adapted from ECASS III as any apparently extravascular blood in the brain or within the cranium that is associated with clinical deterioration as defined by an increase of four points or more in the NIHSS, or that led to death and was judged to be the predominant cause of a neurologic deterioration. The SITS-MOST definition of SICH is: Any PH-2 with a four point or more increase in NIHSS.

Unanticipated Serious Adverse Device Effects (USADEs): A subset of SADEs that are unanticipated, or not previously identified in the labeling of the investigational device, including the Investigator Brochure, Clinical Investigational Plan and Informed Consent Form

Vessel Perforation: A hole or puncture (perforation) in the vessel wall that occurs unintentionally during the index procedure. The perforations may be seen angiographically during the index procedure by frank or free extravasation of the contrast into the surrounding tissue or blush or localized contrast extending outside the vessel lumen.

Weighted mRS: A numerical value representing the clinical utility of each mRS category.

Appendix C. Angiographic Core Lab Scales

TIMI Grade Scale

0 - No perfusion
1 - Penetration with minimal perfusion
2a - Partial perfusion of the artery & its main branches < 50%
2b - Partial perfusion of the artery & its main branches ≥50%
3 - Complete perfusion

Collateral Flow Grade

0 - No collaterals visible to the ischemic site
1 - Slow collaterals to the periphery of the ischemic site with persistence of some of the defect
2 - Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3 - Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4 - Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

AOL Grade

0 - No recanalization of the primary occlusive lesion
I - Incomplete or partial recanalization of the primary occlusive lesion with no distal flow
II - Incomplete or partial recanalization of the primary occlusive lesion with any distal flow
III - Complete recanalization of the primary occlusion with any distal flow

TICI Scale

0 - No Perfusion - No antegrade flow beyond the point of occlusion
1 - Penetration with Minimal Perfusion - The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run
2 - Partial Perfusion - The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction; However, the rate of entry of the contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g. the opposite cerebral artery of the arterial bed proximal to the obstruction

- **2a -** Only partial filling (<2/3) of the entire vascular territory is visualized
- **2b -** Complete filling (≥ 2/3) of all the expected vascular territory is visualized, but the filling is slower than normal

3 - Complete Perfusion - Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery

Modified TICI Scale (mTICI Scale)

0 - No Perfusion - No antegrade flow beyond the point of occlusion

1 - Penetration with Minimal Perfusion - The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run

2 - Partial Perfusion - The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction; However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction

- **2a** - Only partial filling (< 50%) of the entire vascular territory is visualized
- **2b** - Filling of ≥ 50% all of the expected vascular territory is visualized, but the filling is slower than normal

3 - Complete Perfusion - Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

Appendix D. Informed Consent Form Template [attached]

Appendix E. Sample Instructions for Use (IFU) [attached]

Appendix F. Adaptive Design Plan [attached]