

Protocol

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

Protocol for: Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11-21. DOI: 10.1056/NEJMoa1706442

Supplementary Documentation

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Study Duration	<ul style="list-style-type: none"> • Enrollment: approximately 36 months • Subject participation: 90 days (\pm 14) • Total Study Duration: approximately 39 months (+/- 9 months)
Follow-Up Schedule	<p>All follow up time points are relative to time of randomization (time zero):</p> <ol style="list-style-type: none"> 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 <u>blinded</u> mRS (Optional repeat MRI T2/Flair or CT, if MR is contraindicated, may be performed to assess infarct volume) 3. Day 30 (\pm 14): NIHSS and blinded mRS 4. Day 90 (\pm 14): NIHSS and blinded mRS
General Inclusion Criteria	<ol style="list-style-type: none"> 1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, <u>and</u> subject belongs to one of the following subgroups: <ol style="list-style-type: none"> 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 \geq18 3. Baseline NIHSS \geq10 (assessed within one hour prior to 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*
General Inclusion Criteria (additional information)	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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 RAPID MR-DWI or CTP-rCBF maps: <ol style="list-style-type: none"> a. 0-20 cc core infarct and NIHSS \geq 10 (and age \geq 80 years old) b. 0-30 cc core infarct and NIHSS \geq 10 (and age $<$ 80 years old) c. 31 cc to \leq 50 cc core infarct and NIHSS \geq 20 (and age $<$ 80 years old)

* If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if, representative or person of trust is available. 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).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

General Exclusion Criteria	<ol style="list-style-type: none">1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history2. Rapid improvement in neurological status to an NIHSS <10 or evidence of vessel recanalization prior to randomization3. 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 assessment5. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol)6. Renal failure as defined by a serum creatinine >3.0 mg/dL (264 µmol/L) <u>NOTE:</u> subjects on renal dialysis may be treated regardless of serum creatinine levels7. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal; If factor Xa inhibitor (e.g. apixaban) < 24 hrs ago must have normal ecarin clotting time and if 24-48 hrs ago must have normal PTT.8. Any active or recent hemorrhage within the past 30 days9. Baseline platelet count < 50,000/uL10. History of severe allergy (more than rash) to contrast medium11. Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg) <u>NOTE:</u> If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled12. Female who is pregnant or lactating at time of admission13. Current participation in another investigational drug or device study or registry14. Presumed septic embolus, or suspicion of bacterial endocarditis15. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. Evidence of intracranial hemorrhage on CT/MRI2. Evidence of internal carotid artery flow limiting dissection on CTA/MRA3. Severe proximal extra-cranial carotid artery stenosis, or occlusion of any etiology, where concurrent vessel angioplasty or stenting is expected to be necessary and the procedure cannot be delayed until after the 24 (-6/+24) hour assessments have been completed4. Excessive tortuosity of cervical vessels on CTA/MRA that would likely preclude device delivery/deployment5. Suspected cerebral vasculitis based on medical history and CTA/MRA6. Suspected aortic dissection based on medical history and CTA/MRA7. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device8. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Sponsor:	Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515
Study Responsibility:	Cindy Jahans, BSc Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: cindy.jahans@stryker.com Tel: (510) 413-2268 e-Fax: (855) 328-1403
Coordinating Principal Investigators:	Tudor G. Jovin, MD Associate Professor of Neurology and Neurosurgery Director UPMC Stroke Institute UPMC Presbyterian, Fourth Floor, Suite C400 200 Lothrop Street Pittsburgh, PA 15213 Email: jovitg@upmc.edu Tel: (412) 647-4999 or (412) 647-3030 Fax: (412) 647-8445 Raul Nogueira, MD Director of Neuroendovascular Service Marcus Stroke & Neuroscience Center Grady Memorial Hospital Associate Professor of Neurology, Neurosurgery and Radiology Emory University School of Medicine Emory Faculty Office Building 80 Jesse Hill Drive SE Room# 398 Atlanta, GA 30303 Email: raul.g.nogueira@emory.edu Tel: (404) 616-4013 Fax: (404)659-0849
Study Centers:	A current list of sites will be maintained in the Sponsor's Study Files.
Date / Version:	24 Apr 2014 Rev: AA
Date(s) of Amendment(s):	N/A

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. Do not copy or distribute without written permission.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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
Device Sizes	4 mm x 20 mm and 3 mm x 20 mm (additional sizes may be included in the study as they become available)
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	Difference between the average weighted modified Rankin Scale score at 90 days between the active and control groups.
Secondary Endpoints	<ol style="list-style-type: none">Proportion of subjects with a good functional outcome at 90 days, defined as mRS 0-2Proportion 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 1Difference in all cause mortality rates between the two groups.Difference in median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if contraindicated for MR)Difference in revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA.<u>Treatment Arm Only:</u> Analysis of vessel reperfusion rates (percentages) post device and post procedure, by angiography core lab measurement of modified TICI $\geq 2b$

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Primary Safety Outcome	<u>Both Arms:</u> <ol style="list-style-type: none"> 1. Incidence of stroke-related mortality at 90 days 																
Secondary Safety Outcomes	<u>Both Arms:</u> <ol style="list-style-type: none"> 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. <u>Treatment Arm:</u> <ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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 (<i>in vivo</i> breakage) g. any other complications adjudicated by the CEC to be related to the procedure 																
Efficacy Parameter	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 analysis each mRS category will be assigned a numerical value representing its clinical utility, as follows: <table border="1" style="margin-left: auto; margin-right: auto;"> <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>	mRS	0	1	2	3	4	5	6	Weight	10	9.1	7.6	6.5	3.3	0	0
mRS	0	1	2	3	4	5	6										
Weight	10	9.1	7.6	6.5	3.3	0	0										
Randomization	Subjects will be randomized 1:1 to Trevo thrombectomy plus medical management or medical management alone. <u>Stratification will occur by:</u> 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.																

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

	<p>anterior/posterior circulation) as confirmed on CTA/MRA, or clinical evidence of bilateral strokes or strokes in multiple territories</p> <ol style="list-style-type: none"> 9. Significant mass effect with midline shift as confirmed on CT/MRI 10. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI
Concomitant Medication Therapies	<p><u>Treatment Arm:</u></p> <ol style="list-style-type: none"> 1. Use of IV or IA lytics, or 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. <p><u>Medical Management Arm:</u></p> <ol style="list-style-type: none"> 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. <p><u>Both Arms:</u></p> <ol style="list-style-type: none"> 6. Newly administered aspirin is the only anti-platelet 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 regimen after post procedure imaging is completed 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 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 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 weighted 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

1	Introduction and Rationale	12
1.1	Incidence and Burden of Stroke	12
1.2	Current Treatment Options	12
1.3	Unmet Need in Acute Ischemic Stroke	12
1.4	Purpose of Study	14
2	Study Device.....	15
2.1	Study Device Description	15
2.2	Study Device Labeling.....	16
3	Study Objective	17
3.1	Primary Objective	17
3.2	Secondary Objectives.....	17
4	Study Endpoints and Safety Outcomes	17
4.1	Primary Endpoint	17
4.2	Secondary Endpoints.....	18
4.3	Primary Safety Outcome	18
4.4	Secondary Safety Outcomes	18
5	Study Design	19
5.1	Overview	19
5.2	Justification for the Study Design	21
	<i>5.2.1Justification for Expansion of Time Window.....</i>	22
	<i>5.2.2Justification for Inclusion of Wake up and Unclear Onset Strokes</i>	26
	<i>5.2.3Justification for Inclusion of IV tPA Failures.....</i>	26
	<i>5.2.4Justification for Non Reliance on Penumbra Imaging.....</i>	27
	<i>5.2.5Justification for Use of Clinical Imaging Mismatch Criteria.....</i>	28
	<i>5.2.6Justification for Use of Standardized RAPID Imaging Software.....</i>	30
	<i>5.2.7Justification for Use of Weighted mRS as Primary Endpoint.....</i>	30
	<i>5.2.8Justification for Use of Adaptive Design</i>	31
5.3	Method of Assigning Subjects to Treatments	32
5.4	Blinding and Breaking the Blind.....	32
6	Study Population	33
6.1	Inclusion Criteria	33
6.2	Exclusion Criteria	33
6.3	Withdrawal and Replacement of Subjects	34

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

6.4	Enrollment Controls	35
7	Study Procedures.....	35
7.1	Written Informed Consent.....	35
7.2	Prior to Randomization	36
7.3	Angiography Procedure (Treatment arm only)	39
	<i>7.3.1Diagnostic Angiography.....</i>	39
	<i>7.3.2Unexpected Diagnostic Angiography Findings.....</i>	40
7.4	Trevo Thrombectomy Procedure (Treatment arm only)	42
7.5	End of the Trevo Thrombectomy Procedure (Treatment arm only).....	44
7.6	24 (-6 / +24) Hours post Randomization.....	45
7.7	Concomitant Medications and Management.....	45
	<i>7.7.1Blood pressure management.....</i>	46
	<i>7.7.2Glucose management.....</i>	47
7.8	Day 5-7 / Discharge	47
7.9	Post Discharge Follow-up	48
	<i>7.9.1Day 30 (\pm 14).....</i>	48
	<i>7.9.2Day 90 (\pm 14).....</i>	48
8	Statistical Methods	49
8.1	Sample Size Estimate and Justification.....	49
8.2	Control of Systematic Error/Bias	50
8.3	Eligibility of Subjects, Exclusions, and Missing Data	50
8.4	Population Definitions	50
8.5	Analysis Populations.....	51
8.6	Interim Analysis.....	51
	<i>8.6.1Interim Monitoring for Early Futility</i>	52
	<i>8.6.2Enrichment.....</i>	52
	<i>8.6.3Interim Monitoring for Expected Success.....</i>	53
	<i>8.6.4Longitudinal Model.....</i>	53
8.7	Statistical Analysis.....	53
	<i>8.7.1Baseline Comparability</i>	54
	<i>8.7.2Pooling Across Institutions.....</i>	54
	<i>8.7.3Other Pre-planned Analyses</i>	54
	<i>8.7.4Health Economics Information.....</i>	54

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

9	Data Management	55
9.1	Data Collection and Processing	55
10	Monitoring Procedures	55
10.1	Auditing	56
10.2	Investigational Device Accountability	56
11	Adverse Events	56
11.1	Adverse Event Definitions and Classification.....	56
11.2	Adverse Events Reporting Requirements	58
11.3	Device Failures, Malfunctions, and Product Nonconformities	58
11.4	Reporting to Regulatory Authorities / IRBs / ECs / Investigators	59
12	Risk Benefit Analysis.....	59
12.1	CT/MR Imaging.....	59
12.2	Investigational procedure (Treatment arm only).....	60
	<i>12.2.1 ..Diagnostic Angiography</i>	60
	<i>12.2.2 ..Trevo Thrombectomy</i>	61
12.3	Risk Minimization.....	62
13	Study Committees and Core Labs	62
13.1	Steering Committee.....	62
13.2	Safety Monitoring Committees	63
	<i>13.2.1 ..Clinical Events Committee (CEC)</i>	63
	<i>13.2.2 ..Data Monitoring Committee (DMC)</i>	64
13.3	Imaging Core Labs.....	65
	<i>13.3.1 ..Angiographic Core Lab</i>	66
	<i>13.3.2 ..CT/MR Core Lab</i>	66
14	Ethical Considerations	67
14.1	Compliance with Good Clinical Practices (GCP)	67
14.2	Institutional Review Board/ Ethics Committee	67
14.3	Written Informed Consent Form	68
14.4	Amending the Protocol	68
14.5	Protocol Adherence	68
15	Study Administration.....	69
15.1	Pre-Study Documentation Requirements	69
15.2	Record Retention	69

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

15.3	Criteria for Terminating Study	69
15.4	Criteria for Suspending/Terminating a Study Site	69
16	References	70
17	Appendices	75
Appendix A.	Abbreviations.....	75
Appendix B.	Definitions	80
Appendix C.	Angiographic Core Lab Scales	84
Appendix D.	Informed Consent Form Template [attached]	86
Appendix E.	Proposed Instructions for Use (IFU) [attached]	87
Appendix F.	Adaptive Design Plan [attached]	88

List of Figures

Figure 1.	Trevo Retrievers under fluoroscopy.....	16
Figure 2.	DAWN™ Trial Flow Chart	20

List of Tables

Table 1.	Zaidi – Anterior LVOs treated \leq 8 hrs and $>$ 8 hrs after TLSW	23
Table 2.	Merci Registry - Anterior LVOs treated \leq 8 hr and $>$ 8 hr after TLSW	24
Table 3.	Pre-DAWN Cohort vs. PROACT-II Treatment and Control Arm.....	25
Table 4.	DAWN™ Trial Time and Events Schedule	38
Table 5.	Distribution of mRS outcomes for the control arm in the simulations.....	49
Table 6.	Intracranial Hemorrhage Types.....	67

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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, Stentriever™ 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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 unwitnessed 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).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

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.

[Remainder of page is intentionally blank.]

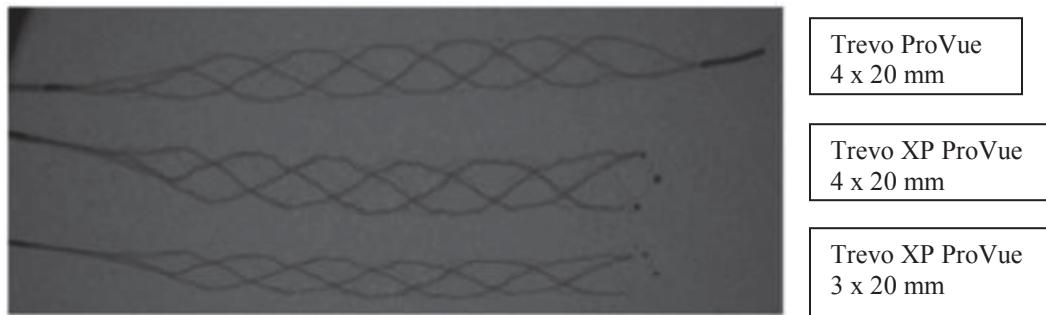
Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Figure 1. Trevo Retrievers under fluoroscopy



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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- 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, and 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 a comparison of the difference between the average weighted modified Rankin Scale (mRS) score at 90 days post randomization between the active and control groups. 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]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 $\geq 2b$.

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- 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 3** shows the flow of subjects through the screening, randomization assignment and follow up phases of the study.

[Remainder of page is intentionally blank.]

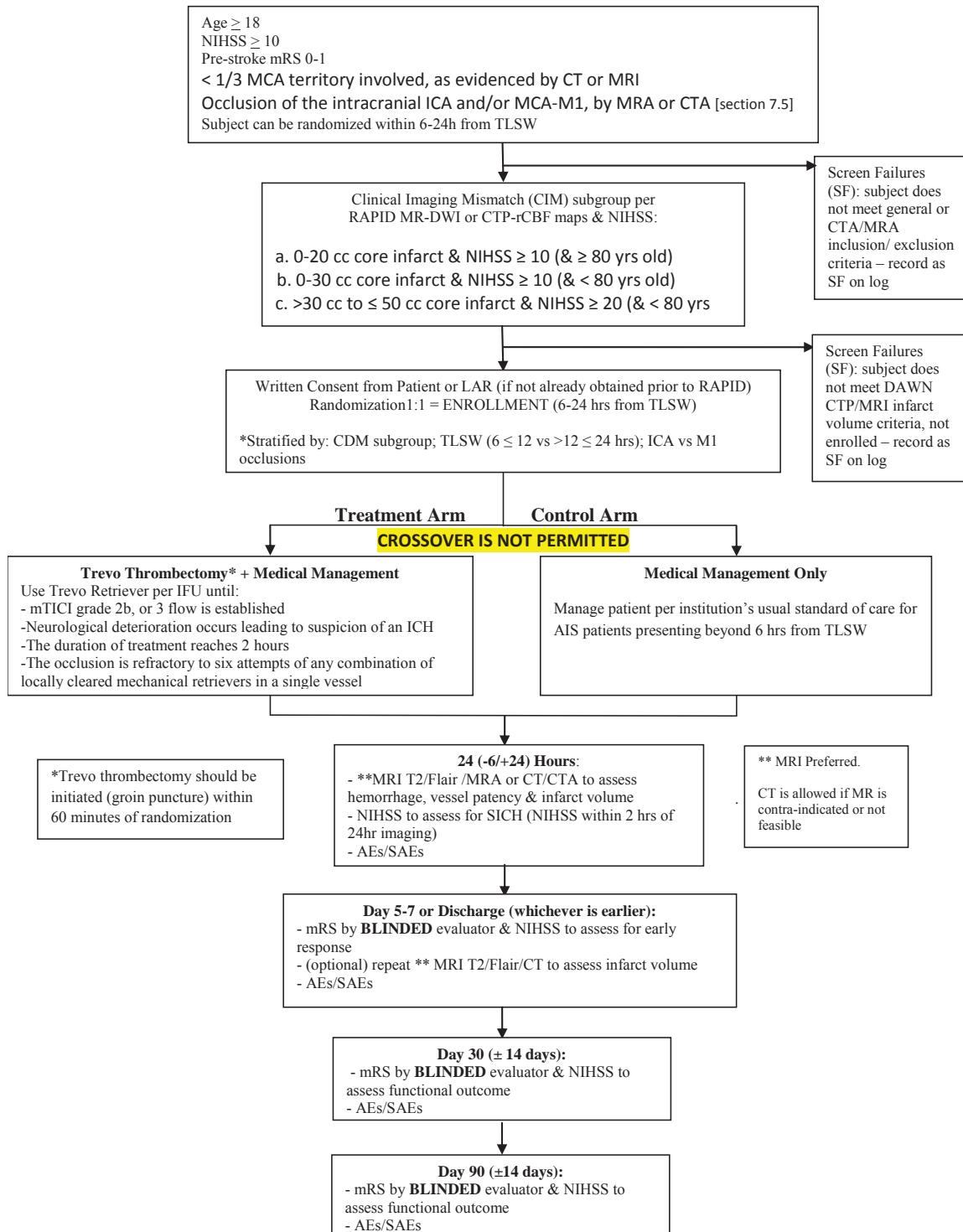
Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Figure 2. DAWN™ Trial Flow Chart



Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 Stentriever™ 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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: ≤ 8 hr (n=123) and >8 hr (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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 1** below. [44]

Table 1. Zaidi – Anterior LVOs treated ≤ 8 hrs and > 8 hrs after TSW

	≤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 TSW. [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 2**.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Table 2. Merci Registry - Anterior LVOs treated \leq 8 hr and $>$ 8 hr after TSWL

Outcomes	0-8 hours (n= 679)	>8 hours (n= 112)	Difference [95% CI]	p-value
Mean TSWL	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 \leq 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 TSWL 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

score ≥ 10 , (2) ICA or MCA-M1 occlusion (with or without cervical occlusion/severe stenosis), and (3) TSW 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 TSW 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 3** 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 3. 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 \pm SD	64 \pm 16	64 \pm 14	64 \pm 14
Median Baseline NIHSS (Min-Max)	17 (10 - 29)	17 (5 - 27)	17 (4 - 28)
Female	54%	42%	39%
TSW 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	0%	35%	37%
MCA-M1	54%	61%	63%
ICA-T	22%	0%	0%
Tandem ICA/MCA	17%	0%	0%
Tandem ICA/ICA-T	7%	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 TSW in appropriately selected subjects.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 infarcted 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

- a. 0-20 cc core infarct and NIHSS ≥ 10 (and ≥ 80 years old)
- b. 0-30 cc core infarct and NIHSS ≥ 10 (and < 80 years old)
- c. 31 cc to ≤ 50 cc core infarct and NIHSS ≥ 20 (and < 80 years old)

5.2.6 Justification for Use of Standardized RAPID 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 RAPID software (iSchemaView, Palo Alto, CA) which will be installed at each site, and on all CT/MR scanners used to screen subjects. **Note:** RAPID software is to be used for research purposes only, and is not to be used for routine clinical assessment of images for patients who are not being screened for the DAWN study.

RAPID 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 rCBF 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 RAPID 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.

The RAPID software has been 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. 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 RAPID 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

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

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 neurothrombectomy, 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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 \leq 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 (RAPID) 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 (\pm 14) and Day 90 (\pm 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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

6 Study Population

6.1 Inclusion Criteria

General Inclusion Criteria	<ol style="list-style-type: none">1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, <u>and</u> subject belongs to one of the following subgroups:<ol style="list-style-type: none">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 administration2. Age ≥ 183. Baseline NIHSS ≥ 10 (assessed within one hour prior to measuring core infarct volume)4. Subject can be randomized between 6 to 24 hours after time last known well5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1)6. Anticipated life expectancy of at least 6 months7. Subject willing/able to return for protocol required follow up visits8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form*
General Inclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. $< 1/3$ MCA territory involved, as evidenced by CT or MRI2. Occlusion of the intracranial ICA and/or MCA-M1 as evidenced by MRA or CTA3. Clinical Imaging Mismatch (CIM) defined as one of the following on RAPID MR-DWI or CTP-rCBF maps:<ol style="list-style-type: none">a. 0-20 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old)b. 0-30 cc core infarct and NIHSS ≥ 10 (and age < 80 years old)c. 31 cc to ≤ 50 cc core infarct and NIHSS ≥ 20 (and age < 80 years old)

* If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if, representative or person of trust is available. 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.)

6.2 Exclusion Criteria

General Exclusion Criteria	<ol style="list-style-type: none">1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history2. Rapid improvement in neurological status to an NIHSS < 10 or evidence of vessel recanalization prior to randomization3. 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 assessment5. Baseline blood glucose of < 50 mg/dL (2.78 mmol) or > 400 mg/dL (22.20 mmol)6. 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
----------------------------	--

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

	<ol style="list-style-type: none">7. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal; If factor Xa inhibitor (e.g. apixaban) < 24 hrs ago must have normal ecarin clotting time and if 24-48 hrs ago must have normal PTT.8. Any active or recent hemorrhage within the past 30 days9. Baseline platelet count < 50,000/uL10. History of severe allergy (more than rash) to contrast medium11. 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 enrolled12. Female who is pregnant or lactating at time of admission13. Current participation in another investigational drug or device study or registry14. Presumed septic embolus, or suspicion of bacterial endocarditis15. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. Evidence of intracranial hemorrhage on CT/MRI2. Evidence of internal carotid artery flow limiting dissection on CTA/MRA3. Severe proximal extra-cranial carotid artery stenosis, or occlusion of any etiology, where concurrent vessel angioplasty or stenting is expected to be necessary and the procedure cannot be delayed until after the 24 (-6/+24) hours assessments have been completed4. Excessive tortuosity of cervical vessels on CTA/MRA that would likely preclude device delivery/deployment5. Suspected cerebral vasculitis based on medical history and CTA/MRA6. Suspected aortic dissection based on medical history and CTA/MRA7. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device8. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) as confirmed on CTA/MRA, or clinical evidence of bilateral strokes or strokes in multiple territories9. Significant mass effect with midline shift as confirmed on CT/MRI10. 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 (\pm 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 4**.

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 if, representative or person of trust is available. 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, either before the routine, standard of care baseline imaging is performed to assess the subject for hemorrhage and large vessel occlusion status, or after the baseline imaging is performed but before the baseline images are sent to the RAPID software to measure the core infarct volume. The Informed Consent Form (ICF) must be approved by the study Institutional Review Board (IRB)/ Ethics Committee (EC). Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent Form, non invasive

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 will be entered into the electronic database and their reason(s) for screen failure will be documented, 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/PT/PTT/INR/blood glucose
- 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.

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 4**, 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- **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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Table 4. 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 or CT (optional)			
AEs/SAEs (from time of randomization)		✓	✓	✓	✓	✓	✓
Concomitant Medications		✓	✓	✓		✓	✓
In Hospital Med Management					✓		
Intubation Details					✓		
UB04 / Health Economics					✓		

*NIHSS should be obtained within 1 hour of corresponding core infarct measurement.

** NIHSS should be obtained within 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.

*** CT/MR and Angiographic images should be de-identified before being submitted to Stryker NV or core lab.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION.
NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

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-

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- B. If thrombus is identified in one or more proximal non treatable arteries per protocol and 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. 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 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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

“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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 8 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- a. If reperfusion has been successful with the Trevo Retriever (defined as at least modified **TICI 2b** 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.

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. Modified TICI grade 2b or 3flow 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Both Arms:

- Newly administered aspirin is the only anti-platelet 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 after post procedure imaging is completed 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 vasoconstrictors to improve cerebral blood flow. If drug induced hypertension is used, close neurological and cardiac monitoring is recommended.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 4**. 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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 \geq 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 5**.

Table 5. 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 RAPID 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).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 RAPID 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 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 analysis 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).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Specifically, the threshold is calculated as:

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

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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**.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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. <i>Note 1:</i> This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. <i>Note 2:</i> This definition includes any event that is a result of a user error.	ISO 14155-1

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Term	Definition	Reference
Serious adverse event (SAE)	<p>An adverse event that:</p> <ul style="list-style-type: none">• 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)	<p>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.</p>	ISO 14155-1
Unanticipated Adverse Device Effect (UADE)	<p>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.</p>	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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

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

Unknown – There is not enough information to make a determination.

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.

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

Unknown – There is not enough information to make a determination.

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. 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 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).

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 thrombectomy 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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. At the time of database lock 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 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. 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 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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

Two central imaging core labs will be established to independently review CT/MR and angiographic images. One lab will review angiographic images from the procedure to determine revascularization and clot location. Another independent 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. Having a CT/MR core lab independent from the angiographic core lab ensures that the CT/MR core lab is blinded to the treatment.

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 Stryker NV for tracking, archiving and forwarding 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 6**.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Core infarct 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 6. 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 \leq 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

Note - If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if, representative or person of trust is available. 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**.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

16 References

1. CDC. *Stroke Facts*. 2013; Available from: <http://www.cdc.gov/stroke.facts.htm>.
2. Roger, V.L., et al., *Heart Disease and Stroke Statistics—2012 Update A Report From the American Heart Association*. Circulation, 2012. **125**(1): p. e2-e220.
3. Smith, W.S., et al., *Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia*. Neurocrit Care, 2006. **4**(1): p. 14-7.
4. Heidenreich, P.A., et al., *Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association*. Circulation, 2011. **123**(8): p. 933-944.
5. Katzen, I.L., et al., *Utilization of intravenous tissue plasminogen activator for acute ischemic stroke*. Arch Neurol, 2004. **61**(3): p. 346-50.
6. Hacke, W., et al., *Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials*. Lancet, 2004. **363**(9411): p. 768-74.
7. Marler, J.R., et al., *Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study*. Neurology, 2000. **55**(11): p. 1649-55.
8. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke*. New England Journal of Medicine, 2008. **359**(13): p. 1317-1329.
9. Bhatia, R., et al., *Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action*. Stroke, 2010. **41**(10): p. 2254-8.
10. Riedel, C.H., et al., *The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length*. Stroke, 2011. **42**(6): p. 1775-7.
11. Smith, W.S., et al., *Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial*. Stroke, 2008. **39**(4): p. 1205-12.
12. Smith, W.S., et al., *Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial*. Stroke, 2005. **36**(7): p. 1432-8.
13. Clark, W., et al., *The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease*. Stroke, 2009. **40**(8): p. 2761-2768.
14. Saver, J.L., et al., *Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial*. The Lancet, 2012. **380**(9849): p. 1241-1249.
15. Nogueira, R.G., et al., *Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial*. The Lancet, 2012. **380**(9849): p. 1231-1240.
16. Alexandrov, A.V., et al., *Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke*. N Engl J Med, 2004. **351**(21): p. 2170-8.
17. Rha, J.H. and J.L. Saver, *The impact of recanalization on ischemic stroke outcome: a meta-analysis*. Stroke, 2007. **38**(3): p. 967-73.
18. Wunderlich, M.T., et al., *Recanalization after intravenous thrombolysis: does a recanalization time window exist?* Neurology, 2007. **68**(17): p. 1364-8.
19. Nogueira, R.G., L.H. Schwamm, and J.A. Hirsch, *Endovascular Approaches to Acute Stroke, Part 1: Drugs, Devices, and Data*. AJNR Am J Neuroradiol, 2009.
20. Nogueira, R.G., et al., *Endovascular approaches to acute stroke, part 2: a comprehensive review of studies and trials*. AJNR Am J Neuroradiol, 2009. **30**(5): p. 859-75.
21. Furlan, A.J., *Clot retrieval for stroke should be restricted to clinical trials: no.* Stroke, 2010. **41**(1): p. 194-5.
22. Hernandez-Perez, *Natural History of Acute Stroke due to Occlusion of the Middle Cerebral Artery and Intracranial Internal Carotid Artery*, in *Journal of Neuroimaging*, e. al, Editor. 2013: (In press at time of this writing).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

23. Gonzalez, R., et al. (2012) *Improved Outcome Prediction Using CT Angiography in Addition to Standard Ischemic Stroke Assessment: Results from the STOPStroke Study*. PLoS ONE 7, e30352 DOI: 10.1371/journal.pone.0030352
24. Janardhan V, G.R., Chen SH, et al. *Preliminary Results from the FIRST Trial: Natural History of Acute Stroke from Large Vessel Occlusion*. in *International Stroke Conference*. 2013. Honolulu, HI: Stroke. 44:A194.
25. Furlan, A., et al., *Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism*. Jama, 1999. **282**(21): p. 2003-11.
26. Ogawa, A., et al., *Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan*. Stroke, 2007. **38**(10): p. 2633-9.
27. Furlan, *Personal Communication to Raul Nogueira re: ProAct II - M1 subgroup good outcomes*, R. Nogueira, Editor. 2013.
28. Nogueira, R.G., et al. *Preliminary Data for the DAWN Trial (DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention): Results of Imaging-Based Endovascular Therapy for Proximal Anterior Circulation Occlusions beyond 8 Hours from Last Seen Well in 237 Stroke Patients*. in *Society of Neurointerventional Surgery (SNIS) 6th Annual Meeting*. 2009. Boca Raton, Florida.
29. Jauch EC, S.J., Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H *Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association*. Stroke, 2013.
30. Kleindorfer, D., et al., *Emergency Department Arrival Times after Acute Ischemic Stroke During the 1990s*. Neurocritical Care, 2007. **7**(1): p. 31-35.
31. Fink, J.N., et al., *The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI*. Stroke, 2002. **33**(4): p. 988-93.
32. Silva, G.S., et al., *Wake-up stroke: clinical and neuroimaging characteristics*. Cerebrovasc Dis, 2010. **29**(4): p. 336-42.
33. Todo, K., et al., *Early CT findings in unknown-onset and wake-up strokes*. Cerebrovasc Dis, 2006. **21**(5-6): p. 367-71.
34. Adams, H.P., Jr., et al., *Treating patients with 'wake-up' stroke: the experience of the AbESTT-II trial*. Stroke, 2008. **39**(12): p. 3277-82.
35. Barreto, A.D., et al., *Thrombolytic therapy for patients who wake-up with stroke*. Stroke, 2009. **40**(3): p. 827-32.
36. Cho, A.H., et al., *Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke. A preliminary report*. Cerebrovasc Dis, 2008. **25**(6): p. 572-9.
37. Copen, W.A., et al., *Existence of the diffusion-perfusion mismatch within 24 hours after onset of acute stroke: dependence on proximal arterial occlusion*. Radiology, 2009. **250**(3): p. 878-86.
38. Jovin, T.G., et al., *Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients*. Stroke, 2011. **42**(8): p. 2206-11.
39. Thomalla, G., et al., *Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials*. Stroke, 2006. **37**(3): p. 852-8.
40. Kohrmann, M., et al., *MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: a cohort study*. Lancet Neurol, 2006. **5**(8): p. 661-7.
41. Schellinger, P.D., et al., *MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients*. Stroke, 2007. **38**(10): p. 2640-5.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

42. Janjua, N., et al., *Late endovascular revascularization in acute ischemic stroke based on clinical-diffusion mismatch.* AJNR Am J Neuroradiol, 2009. **30**(5): p. 1024-7.
43. Natarajan, S.K., et al., *Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes.* Stroke, 2009. **40**(10): p. 3269-74.
44. Zaidi, S., et al. *Intra-arterial Treatment for Acute Anterior Circulation Ischemic Strokes Due to Large Vessel Occlusion Beyond 8 Hours – Preliminary Results.* in European Stroke Conference. 2008. Nice, France.
45. Rai, A.T., et al., *Endovascular therapy yields significantly superior outcomes for large vessel occlusions compared with intravenous thrombolysis: is it time to randomize?* Journal of NeuroInterventional Surgery, 2012.
46. Rai, A.T., et al., *Pre-intervention triage incorporating perfusion imaging improves outcomes in patients undergoing endovascular stroke therapy: a comparison with the device trials.* Journal of NeuroInterventional Surgery, 2013. **5**(2): p. 121-127.
47. Turk, A.S., et al., *Utilization of CT perfusion patient selection for mechanical thrombectomy irrespective of time: a comparison of functional outcomes and complications.* Journal of NeuroInterventional Surgery, 2012.
48. Rivero-Arias, O., et al., *Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome.* Medical decision making, 2010. **30**(3): p. 341-354.
49. Hong, K.-S. and J.L. Saver, *Quantifying the Value of Stroke Disability Outcomes WHO Global Burden of Disease Project Disability Weights for Each Level of the Modified Rankin Scale.* Stroke, 2009. **40**(12): p. 3828-3833.
50. Castano, C., et al., *Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation: a pilot study.* Stroke, 2010. **41**(8): p. 1836-40.
51. Roth, C., et al., *Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions.* Stroke, 2010. **41**(11): p. 2559-2567.
52. Mpotaris, A., et al., *Mechanical thrombectomy in severe acute stroke: preliminary results of the Solitaire stent.* Journal of Neurology, Neurosurgery & Psychiatry, 2012. **83**(1): p. 117-118.
53. Galimianis, A., et al., *Endovascular therapy of 623 patients with anterior circulation stroke.* Stroke, 2012. **43**(4): p. 1052-1057.
54. Flint, A.C., et al., *Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials.* Stroke, 2007. **38**(4): p. 1274-80.
55. Tarr, R., et al., *The POST Trial: Initial Post-Market Experience of the Penumbra System: Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke in the United States and Europe.* Journal of NeuroInterventional Surgery, 2010. **2**(): p. 341-344.
56. Dávalos, A., et al., *Retrospective multicenter study of Solitaire FR for revascularization in the treatment of acute ischemic stroke.* Stroke, 2012. **43**(10): p. 2699-2705.
57. Wahlgren, N., et al. *Final Results From The Trevo Study (Thrombectomy REvascularization of large Vessel Occlusions in acute ischemic stroke).* in International Stroke Conference. 2012. New Orleans, LA.
58. Broderick, J.P., et al., *Endovascular therapy after intravenous t-pa versus t-pa alone for stroke.* New England Journal of Medicine, 2013. **368**(10): p. 893-903.
59. Kidwell, C.S., et al., *A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke.* New England Journal of Medicine, 2013. **368**(10): p. 914-923.
60. Ciccone, A., et al., *Endovascular Treatment for Acute Ischemic Stroke.* New England Journal of Medicine, 2013. **368**(10): p. 904-913.
61. Albuquerque, F.C., et al., *The tribulations of stroke trials.* Journal of NeuroInterventional Surgery, 2013. **5**(3): p. 181-183.
62. SIR. *Society of Interventional Radiologists letter re: Use of Thrombectomy Devies for the Emergent Treatment of Acute Ischemic Stroke.* 2013; Available from: <http://www.sirweb.org/misc/SIRLetter%20CTAF%20STROKE%20Mar2013.pdf>.
63. Wisco, *Addition of MRI for Patient Selection in Intra-arterial Stroke Therapy Leads to Better Clinical Outcomes, a Pre-Post Study in International Stroke Conference Oral Abstracts; A161.* 2012.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

64. Kidwell, C.S., J.R. Alger, and J.L. Saver, *Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging*. Stroke, 2003. **34**(11): p. 2729-35.
65. Donnan, G.A., et al., *Penumbral selection of patients for trials of acute stroke therapy*. Lancet Neurol, 2009. **8**(3): p. 261-9.
66. Saver, J.L., *Time is brain--quantified*. Stroke, 2006. **37**(1): p. 263-6.
67. Leiva-Salinas, C., et al., *Tissue at risk in acute stroke patients treated beyond 8 h after symptom onset*. Neuroradiology, 2013: p. 1-6.
68. Abou-Chebl, A., *Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients*. Stroke, 2010. **41**(9): p. 1996-2000.
69. Wechsler, L.R., et al., *Factors influencing outcome and treatment effect in PROACT II*. Stroke, 2003. **34**(5): p. 1224-9.
70. Khatri, P., et al., *Good clinical outcome after ischemic stroke with successful revascularization is time-dependent*. Neurology, 2009. **73**(13): p. 1066-72.
71. Nogueira, R.G., et al., *Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials*. Stroke, 2009. **40**(12): p. 3777-83.
72. Nogueira, R.G., et al. *Endovascular Therapy for AIS Due to Proximal Arterial Occlusion Treated Beyond 8 Hours from Time Last Seen Well: A Subset Analysis of the Merci Registry*. in Eighth Society of NeuroInterventional Surgery (SNIS) Annual Meeting. 2011. Colorado Springs, Colorado, USA.
73. Jung, S., et al., *Safety of endovascular treatment beyond the 6-h time window in 205 patients*. European Journal of Neurology, 2013.
74. Nogueira, R.G., et al., *Neither Time to Treatment Nor the Use of Adjunctive Intra-arterial Thrombolytics Increase the Risk for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of CT Perfusion or MRI-selected Stroke Patients Treated at Late Time Windows: Analysis of the Pre-DAWN Dataset*. ISC:A93. 2010: Austin, Tx.
75. STAIR. *Stroke Treatment Academic Industry Roundtable*. March 9-10, 2013. Washington D.C. "Accelerating the Evolution of Stroke Therapy". In Press. 2013.
76. Wolpert, S.M., et al., *Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator*. The rt-PA Acute Stroke Study Group. AJNR Am J Neuroradiol, 1993. **14**(1): p. 3-13.
77. Shi, Z.-S., et al., *Endovascular Thrombectomy for Acute Ischemic Stroke in Failed Intravenous Tissue Plasminogen Activator Versus Non-Intravenous Tissue Plasminogen Activator Patients Revascularization and Outcomes Stratified by the Site of Arterial Occlusions*. Stroke, 2010. **41**(6): p. 1185-1192.
78. Davalos, A., et al., *The clinical-DWI mismatch: a new diagnostic approach to the brain tissue at risk of infarction*. Neurology, 2004. **62**(12): p. 2187-92.
79. Ebinger, M., et al., *Clinical-diffusion mismatch and benefit from thrombolysis 3 to 6 hours after acute stroke*. Stroke, 2009. **40**(7): p. 2572-4.
80. Lansberg, M.G., et al., *Evaluation of the clinical-diffusion and perfusion-diffusion mismatch models in DEFUSE*. Stroke, 2007. **38**(6): p. 1826-30.
81. Nogueira, R.G., et al., *Clinical-Diffusion Mismatch Better Discriminates Infarct Growth than MTT-DWI Mismatch in Patients with MCA-M1 Occlusion and Limited Infarct Core*. AJNR, 2013 (Submitted March).
82. Prosser, J., et al., *Clinical-diffusion mismatch predicts the putative penumbra with high specificity*. Stroke, 2005. **36**(8): p. 1700-4.
83. Albers, G.W., et al., *Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study*. Ann Neurol, 2006. **60**(5): p. 508-17.
84. Lansberg, M.G., et al., *Results of DEFUSE 2: Imaging Endpoints*. Stroke.2012;43:A52, 2012.
85. Mishra, N.K., et al., *Mismatch-based delayed thrombolysis: a meta-analysis*. Stroke, 2010. **41**(1): p. e25-33.
86. Dani, K.A., et al., *Systematic review of perfusion imaging with computed tomography and magnetic resonance in acute ischemic stroke: heterogeneity of acquisition and postprocessing parameters: a*

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- translational medicine research collaboration multicentre acute stroke imaging study.* Stroke, 2012. **43**(2): p. 563-6.
87. Goyal, M., B.K. Menon, and C.P. Derdeyn, *Perfusion Imaging in Acute Ischemic Stroke: Let Us Improve the Science before Changing Clinical Practice.* Radiology, 2013. **266**(1): p. 16-21.
88. Jovin, T.G., et al., *The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion.* Stroke, 2003. **34**(10): p. 2426-33.
89. Nogueira, R.G., et al., *Infarct Volume Thresholds for Prediction of Independent Functional Outcomes after Acute Ischemic Stroke.* Stroke 2012. **43**: p. A4030.
90. Lansberg, M.G., et al., *MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study.* The Lancet Neurology, 2012.
91. Zaidi, S.F., et al., *Final infarct volume is a stronger predictor of outcome than recanalization in patients with proximal middle cerebral artery occlusion treated with endovascular therapy.* Stroke, 2012. **43**(12): p. 3238-3244.
92. Furlan, *Personal Communication to Tudor Jovin re: ProAct II - Outcomes by Occlusion Location and NIHSS.* T. Jovin, Editor. 2013.
93. Fischer, U., et al., *NIHSS score and arteriographic findings in acute ischemic stroke.* Stroke, 2005. **36**(10): p. 2121-5.
94. Lewandowski, C.A., et al., *Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial.* Stroke, 1999. **30**(12): p. 2598-605.
95. DeGraba, T.J., et al., *Progression in acute stroke value of the initial NIH Stroke Scale score on patient stratification in future trials.* Stroke, 1999. **30**(6): p. 1208-1212.
96. Ringleb, P.A., et al., *Thrombolytic therapy for acute ischaemic stroke in octogenarians: selection by magnetic resonance imaging improves safety but does not improve outcome.* Journal of Neurology, Neurosurgery & Psychiatry, 2007. **78**(7): p. 690-693.
97. Mishra, N.K., et al., *Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA).* Stroke, 2010. **41**(12): p. 2840-8.
98. Bath, P.M., et al., *Statistical analysis of the primary outcome in acute stroke trials.* Stroke, 2012. **43**(4): p. 1171-1178.
99. Fisher, M., et al., *Stroke Therapy Academic Industry Roundtable IV. Enhancing the development and approval of acute stroke therapies: stroke therapy academic industry roundtable.* Stroke, 2005. **36**(8): p. 1808-1813.
100. Krams, M., K.R. Lees, and D.A. Berry, *The Past Is the Future Innovative Designs in Acute Stroke Therapy Trials.* Stroke, 2005. **36**(6): p. 1341-1347.
101. Shuaib, A., et al., *Partial Aortic Occlusion for Cerebral Perfusion Augmentation Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke Trial.* Stroke, 2011. **42**(6): p. 1680-1690.
102. Kaufmann, e.a., *Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients.* Radiology, 2007. **243**: p. 812-819.
103. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.* N Engl J Med, 2008. **359**(13): p. 1317-29.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

- NOTE 2 – A planned hospitalization for a pre-existing condition or a condition required by the protocol, without serious deterioration in health is not considered serious.

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

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 \geq 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 (\geq 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 unininvolved other bed of the same vessel or the opposite cerebral artery

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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 $\geq 50\%$ 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 unininvolved other bed of the same vessel or the opposite cerebral artery.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Appendix D. Informed Consent Form Template [attached]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AA

Appendix F. Adaptive Design Plan [attached]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Sponsor:	Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515
Study Responsibility:	Christine Yang Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: christine.yang@stryker.com Tel: (510) 413-2841 e-Fax: (855) 328-1403
Coordinating Principal Investigators:	Tudor G. Jovin, MD Associate Professor of Neurology and Neurosurgery Director UPMC Stroke Institute UPMC Presbyterian, Fourth Floor, Suite C400 200 Lothrop Street Pittsburgh, PA 15213 Email: jovitg@upmc.edu Tel: (412) 647-4999 or (412) 647-3030 Fax: (412) 647-8445 Raul Nogueira, MD Director of Neuroendovascular Service Marcus Stroke & Neuroscience Center Grady Memorial Hospital Associate Professor of Neurology, Neurosurgery and Radiology Emory University School of Medicine Emory Faculty Office Building 80 Jesse Hill Drive SE Room# 398 Atlanta, GA 30303 Email: paul.g.nogueira@emory.edu Tel: (404) 616-4013 Fax: (404) 659-0849
Study Centers:	A current list of sites will be maintained in the Sponsor's Study Files.
Date / Version:	24 Apr 2014 Rev: AA
Date(s) of Amendment(s):	14 Sep 2015 Rev: AB

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. Do not copy or distribute without written permission.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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	Difference between the average weighted modified Rankin Scale score at 90 days between the active and control groups.
Secondary Endpoints	<ol style="list-style-type: none">1. Proportion of subjects with a good functional outcome at 90 days, defined as mRS 0-22. 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 13. 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. <u>Treatment Arm Only:</u> Analysis of vessel reperfusion rates (percentages) post device and post procedure, by angiography core lab measurement of modified TICI $\geq 2b$

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Primary Safety Outcome	<u>Both Arms:</u> <ol style="list-style-type: none"> 1. Incidence of stroke-related mortality at 90 days 																
Secondary Safety Outcomes	<u>Both Arms:</u> <ol style="list-style-type: none"> 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. <u>Treatment Arm:</u> <ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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 (<i>in vivo</i> breakage) g. any other complications adjudicated by the CEC to be related to the procedure 																
Efficacy Parameter	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 analysis each mRS category will be assigned a numerical value representing its clinical utility, as follows: <table border="1" style="margin-left: auto; margin-right: auto;"> <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>	mRS	0	1	2	3	4	5	6	Weight	10	9.1	7.6	6.5	3.3	0	0
mRS	0	1	2	3	4	5	6										
Weight	10	9.1	7.6	6.5	3.3	0	0										
Randomization	Subjects will be randomized 1:1 to Trevo thrombectomy plus medical management or medical management alone. <u>Stratification will occur by:</u> 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.																

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Study Duration	<ul style="list-style-type: none"> • Enrollment: approximately 36 months • Subject participation: 90 days (\pm 14) • Total Study Duration: approximately 39 months (+/- 9 months)
Follow-Up Schedule	<p>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.</p> <ol style="list-style-type: none"> 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 <u>blinded</u> mRS (Optional repeat MRI T2/Flair or CT, if MR is contraindicated, may be performed to assess infarct volume) 3. Day 30 (\pm 14): NIHSS and blinded mRS 4. Day 90 (\pm 14): NIHSS and blinded mRS
General Inclusion Criteria	<ol style="list-style-type: none"> 1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, <u>and</u> subject belongs to one of the following subgroups: <ol style="list-style-type: none"> 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 \geq18 3. Baseline NIHSS \geq10 (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* <p>* 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.)</p>
General Inclusion Criteria (additional information)	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> a. 0-<21 cc core infarct and NIHSS \geq 10 (and age \geq 80 years old) b. 0-<31 cc core infarct and NIHSS \geq 10 (and age < 80 years old) c. 31 cc to <51 cc core infarct and NIHSS \geq 20 (and age < 80 years old)

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

General Exclusion Criteria	<ol style="list-style-type: none">1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history2. Rapid improvement in neurological status to an NIHSS <10 or evidence of vessel recanalization prior to randomization3. 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 assessment5. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol)6. Baseline hemoglobin counts of <7 mmol/L7. Baseline platelet count < 50,000/uL8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L9. 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 levels10. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal. Patients on factor Xa inhibitor for 24-48 hours ago must have a normal PTT.11. Any active or recent hemorrhage within the past 30 days12. History of severe allergy (more than rash) to contrast medium13. 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 enrolled14. Female who is pregnant or lactating at time of admission15. Current participation in another investigational drug or device study16. Presumed septic embolus, or suspicion of bacterial endocarditis17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	<ol style="list-style-type: none">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. 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	<ol style="list-style-type: none">1. Evidence of intracranial hemorrhage on CT/MRI2. 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/deployment4. Suspected cerebral vasculitis based on medical history and CTA/MRA5. Suspected aortic dissection based on medical history and CTA/MRA6. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device7. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior circulation/vertebrobasilar system) as confirmed on CTA/MRA, or clinical

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

	<p>evidence of bilateral strokes or strokes in multiple territories</p> <p>8. Significant mass effect with midline shift as confirmed on CT/MRI</p> <p>9. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI</p>
Concomitant Medication Therapies	<p><u>Treatment Arm:</u></p> <p>1. Use of IV or IA lytics, or IV or IA antiplatelets is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed.</p> <p>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.</p> <p>3. Prudent use of anti-vasospasm agents is permitted during the procedure.</p> <p><u>Medical Management Arm:</u></p> <p>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.</p> <p>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.</p> <p><u>Both Arms:</u></p> <p>6. Aspirin 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.</p> <p>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.</p> <p>8. Subcutaneous Low Molecular Weight (LMW) heparin is allowed for Deep Vein Thrombosis (DVT) prophylaxis per the center's standard of care.</p>
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 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 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 weighted 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

1	Introduction and Rationale	12
1.1	Incidence and Burden of Stroke	12
1.2	Current Treatment Options	12
1.3	Unmet Need in Acute Ischemic Stroke	12
1.4	Purpose of Study	14
2	Study Device.....	14
2.1	Study Device Description	14
2.2	Study Device Labeling	16
3	Study Objective	17
3.1	Primary Objective	17
3.2	Secondary Objectives.....	17
4	Study Endpoints and Safety Outcomes	17
4.1	Primary Endpoint	17
4.2	Secondary Endpoints.....	18
4.3	Primary Safety Outcome	18
4.4	Secondary Safety Outcomes	18
5	Study Design	19
5.1	Overview.....	19
5.2	Justification for the Study Design	22
	<i>5.2.1Justification for Expansion of Time Window</i>	23
	<i>5.2.2Justification for Inclusion of Wake up and Unclear Onset Strokes</i>	27
	<i>5.2.3Justification for Inclusion of IV tPA Failures</i>	27
	<i>5.2.4Justification for Non Reliance on Penumbra Imaging</i>	28
	<i>5.2.5Justification for Use of Clinical Imaging Mismatch Criteria</i>	29
	<i>5.2.6Justification for Use of Standardized Core Infarct Imaging Software</i>	31
	<i>5.2.7Justification for Use of Weighted mRS as Primary Endpoint</i>	31
	<i>5.2.8Justification for Use of Adaptive Design</i>	32
5.3	Method of Assigning Subjects to Treatments	33
5.4	Blinding and Breaking the Blind.....	33
6	Study Population	34
6.1	Inclusion Criteria	34
6.2	Exclusion Criteria	34
6.3	Withdrawal and Replacement of Subjects	36

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

6.4	Enrollment Controls	36
7	Study Procedures.....	36
7.1	Written Informed Consent.....	36
7.2	Prior to Randomization	37
7.3	Angiography Procedure (Treatment arm only)	40
	<i>7.3.1Diagnostic Angiography.....</i>	40
	<i>7.3.2Unexpected Diagnostic Angiography Findings.....</i>	41
7.4	Trevo Thrombectomy Procedure (Treatment arm only)	43
7.5	End of the Trevo Thrombectomy Procedure (Treatment arm only).....	45
7.6	24 (-6 / +24) Hours post Randomization.....	46
7.7	Concomitant Medications and Management.....	46
	<i>7.7.1Blood pressure management.....</i>	48
	<i>7.7.2Glucose management.....</i>	49
7.8	Day 5-7 / Discharge	49
7.9	Post Discharge Follow-up.....	50
	<i>7.9.1Day 30 (\pm 14).....</i>	50
	<i>7.9.2Day 90 (\pm 14).....</i>	50
8	Statistical Methods	51
8.1	Sample Size Estimate and Justification.....	51
8.2	Control of Systematic Error/Bias	52
8.3	Eligibility of Subjects, Exclusions, and Missing Data	52
8.4	Population Definitions	52
8.5	Analysis Populations.....	53
8.6	Interim Analysis.....	53
	<i>8.6.1Interim Monitoring for Early Futility</i>	54
	<i>8.6.2Enrichment.....</i>	54
	<i>8.6.3Interim Monitoring for Expected Success.....</i>	55
	<i>8.6.4Longitudinal Model.....</i>	55
8.7	Statistical Analysis.....	55
	<i>8.7.1Baseline Comparability</i>	56
	<i>8.7.2Pooling Across Institutions.....</i>	56
	<i>8.7.3Other Pre-planned Analyses</i>	56
	<i>8.7.4Health Economics Information.....</i>	56

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

9	Data Management	57
9.1	Data Collection and Processing	57
10	Monitoring Procedures	57
10.1	Auditing	58
10.2	Investigational Device Accountability	58
11	Adverse Events	58
11.1	Adverse Event Definitions and Classification.....	58
11.2	Adverse Events Reporting Requirements	60
11.3	Device Failures, Malfunctions, and Product Nonconformities	60
11.4	Reporting to Regulatory Authorities / IRBs / ECs / Investigators	61
12	Risk Benefit Analysis.....	61
12.1	CT/MR Imaging.....	62
12.2	Investigational procedure (Treatment arm only).....	62
	<i>12.2.1 ..Diagnostic Angiography</i>	62
	<i>12.2.2 ..Trevo Thrombectomy</i>	63
12.3	Risk Minimization.....	64
13	Study Committees and Core Labs	65
13.1	Steering Committee.....	65
13.2	Safety Monitoring Committees	65
	<i>13.2.1 ..Clinical Events Committee (CEC)</i>	65
	<i>13.2.2 ..Data Monitoring Committee (DMC)</i>	66
13.3	Imaging Core Labs.....	67
	<i>13.3.1 ..Angiographic Core Lab</i>	68
	<i>13.3.2 ..CT/MR Core Lab</i>	69
14	Ethical Considerations	69
14.1	Compliance with Good Clinical Practices (GCP)	69
14.2	Institutional Review Board/ Ethics Committee	70
14.3	Written Informed Consent Form	70
14.4	Amending the Protocol	71
14.5	Protocol Adherence	71
15	Study Administration.....	71
15.1	Pre-Study Documentation Requirements	71
15.2	Record Retention	71

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

15.3	Criteria for Terminating Study	72
15.4	Criteria for Suspending/Terminating a Study Site	72
16	References	73
17	Appendices	78
Appendix A.	Abbreviations.....	78
Appendix B.	Definitions	83
Appendix C.	Angiographic Core Lab Scales	88
Appendix D.	Informed Consent Form Template [attached]	90
Appendix E.	Sample Instructions for Use (IFU) [attached]	91
Appendix F.	Adaptive Design Plan [attached]	92

List of Figures

Figure 1.	Trevo Retrievers	16
Figure 2.	DAWN™ Trial Flow Chart	20

List of Tables

Table 1.	Key Dimensions of Trevo Family Retrievers	15
Table 2.	Zaidi - Anterior LVOs treated \leq 8 hrs and $>$ 8 hrs after TLSW	24
Table 3.	Merci Registry - Anterior LVOs treated \leq 8 hr and $>$ 8 hr after TLSW	25
Table 4.	Pre-DAWN Cohort vs. PROACT II Treatment and Control Arm.....	26
Table 5.	DAWN™ Trial Time and Events Schedule.....	39
Table 6.	Distribution of mRS outcomes for the control arm in the simulations	51
Table 7.	Intracranial Hemorrhage Types	69

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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, Stentriever™ 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]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 unwitnessed 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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	180cm	20mm	37mm	4mm
Trevo XP ProVue Retrievers					
3x20mm	90192	190cm	20mm	36mm	3mm
4x20mm	90193	180cm	20mm	32mm	4mm
6x25mm	90194	180cm	25mm	40mm	6mm
4x30mm	90195	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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

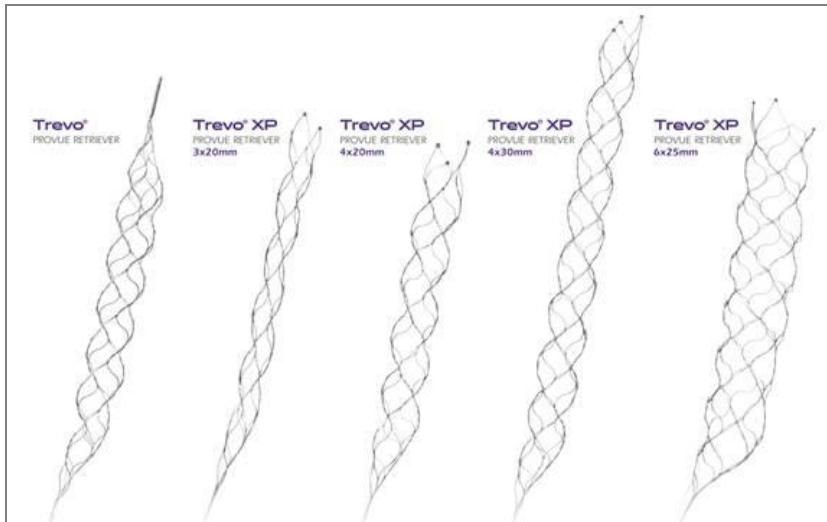
Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

- 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 a comparison of the difference between the average weighted modified Rankin Scale (mRS) score at 90 days post randomization between the active and

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

control groups. 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 $\geq 2b$.

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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

- 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.

[Remainder of page is intentionally blank.]

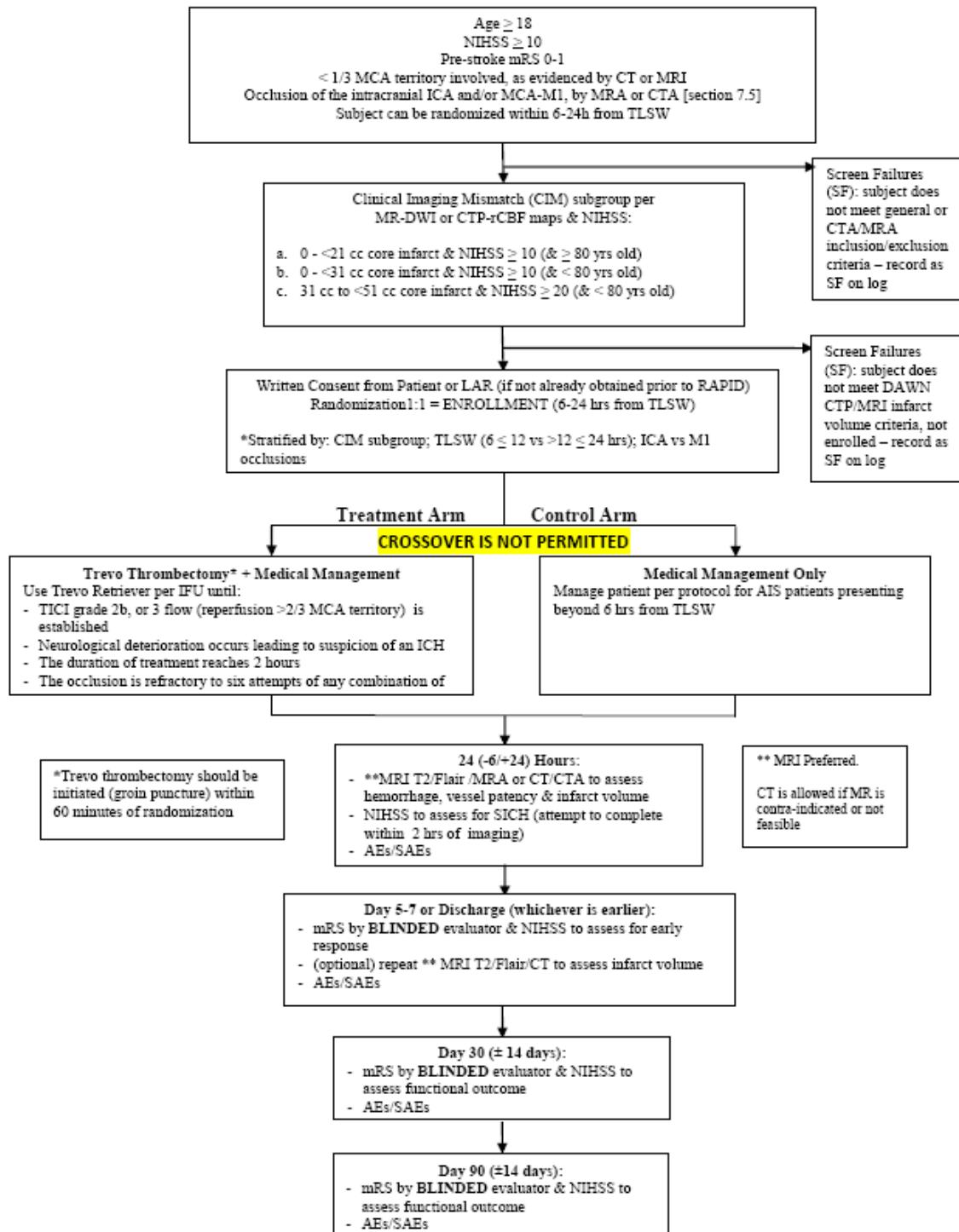
Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Figure 2. DAWN™ Trial Flow Chart



STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 Stentriever™ 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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: ≤ 8 hr (n=123) and >8 hr (n=37). All patients had <1/3 MCA territory hypodensity on baseline head CT and all

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Table 3. Merci Registry - Anterior LVOs treated \leq 8 hr and $>$ 8 hr after TSWL

Outcomes	0-8 hours (n= 679)	>8 hours (n= 112)	Difference [95% CI]	p-value
Mean TSWL	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 \leq 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 TSWL and SICH. [74]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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) TSW 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 TSW 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 \pm SD	64 \pm 16	64 \pm 14	64 \pm 14
Median Baseline NIHSS (Min-Max)	17 (10 - 29)	17 (5 - 27)	17 (4 - 28)
Female	54%	42%	39%
TSW 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	0%	35%	37%
MCA-M1	54%	61%	63%
ICA-T	22%	0%	0%
Tandem ICA/MCA	17%	0%	0%
Tandem ICA/ICA-T	7%	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 TSW in appropriately selected subjects.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 infarcted 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 \leq 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 (\pm 14) and Day 90 (\pm 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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

6 Study Population

6.1 Inclusion Criteria

General Inclusion Criteria	<ol style="list-style-type: none">1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups:<ol style="list-style-type: none">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 administration2. Age ≥ 183. 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 well5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1)6. Anticipated life expectancy of at least 6 months7. Subject willing/able to return for protocol required follow up visits8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form*
General Inclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. $< 1/3$ MCA territory involved, as evidenced by CT or MRI2. Occlusion of the intracranial ICA and/or MCA-M1 as evidenced by MRA or CTA3. Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps:<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history2. Rapid improvement in neurological status to an NIHSS < 10 or evidence of vessel recanalization prior to randomization3. 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 assessment5. Baseline blood glucose of < 50 mg/dL (2.78 mmol) or > 400 mg/dL (22.20 mmol)
----------------------------	--

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

	<ol style="list-style-type: none">6. Baseline hemoglobin counts of <7 mmol/L7. Baseline platelet count < 50,000/uL8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L9. 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 levels10. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal. Patients on factor Xa inhibitor for 24-48 hours ago must have a normal PTT.11. Any active or recent hemorrhage within the past 30 days12. History of severe allergy (more than rash) to contrast medium13. 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 enrolled14. Female who is pregnant or lactating at time of admission15. Current participation in another investigational drug or device study16. Presumed septic embolus, or suspicion of bacterial endocarditis17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. Evidence of intracranial hemorrhage on CT/MRI2. 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/deployment4. Suspected cerebral vasculitis based on medical history and CTA/MRA5. Suspected aortic dissection based on medical history and CTA/MRA6. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device7. 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 territories8. Significant mass effect with midline shift as confirmed on CT/MRI9. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 (\pm 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

(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/PT/PTT/INR/blood glucose
- 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.

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:

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

- **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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 IV 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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

- 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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Both Arms:

- Newly administered aspirin 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 vasoconstrictors to improve cerebral blood flow. If drug induced hypertension is used, close neurological and cardiac monitoring is recommended.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 (\pm 14) follow-up assessments. Requirements of each follow-up evaluation are detailed below.

7.9.1 Day 30 (\pm 14)

At Day 30 (\pm 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 \pm 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 (\pm 14)

At Day 90 (\pm 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 \pm 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 \geq 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 completed their study participation, 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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

- 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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 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 analysis 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).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Specifically, the threshold is calculated as:

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

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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**.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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. <i>Note 1:</i> This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. <i>Note 2:</i> This definition includes any event that is a result of a user error.	ISO 14155-1

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Term	Definition	Reference
Serious adverse event (SAE)	An adverse event that: <ul style="list-style-type: none">• 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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 deaths shall be reported to the IRB no later than 24-48 hours of becoming aware. 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 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.

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**.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 thrombectomy 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

- 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 infarct 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 \leq 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.)

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

16 References

1. CDC. *Stroke Facts*. 2013; Available from: <http://www.cdc.gov/stroke.facts.htm>.
2. Roger, V.L., et al., *Heart Disease and Stroke Statistics—2012 Update A Report From the American Heart Association*. Circulation, 2012. **125**(1): p. e2-e220.
3. Smith, W.S., et al., *Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia*. Neurocrit Care, 2006. **4**(1): p. 14-7.
4. Heidenreich, P.A., et al., *Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association*. Circulation, 2011. **123**(8): p. 933-944.
5. Katzan, I.L., et al., *Utilization of intravenous tissue plasminogen activator for acute ischemic stroke*. Arch Neurol, 2004. **61**(3): p. 346-50.
6. Hacke, W., et al., *Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials*. Lancet, 2004. **363**(9411): p. 768-74.
7. Marler, J.R., et al., *Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study*. Neurology, 2000. **55**(11): p. 1649-55.
8. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke*. New England Journal of Medicine, 2008. **359**(13): p. 1317-1329.
9. Bhatia, R., et al., *Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action*. Stroke, 2010. **41**(10): p. 2254-8.
10. Riedel, C.H., et al., *The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length*. Stroke, 2011. **42**(6): p. 1775-7.
11. Smith, W.S., et al., *Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial*. Stroke, 2008. **39**(4): p. 1205-12.
12. Smith, W.S., et al., *Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial*. Stroke, 2005. **36**(7): p. 1432-8.
13. Clark, W., et al., *The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease*. Stroke, 2009. **40**(8): p. 2761-2768.
14. Saver, J.L., et al., *Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial*. The Lancet, 2012. **380**(9849): p. 1241-1249.
15. Nogueira, R.G., et al., *Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial*. The Lancet, 2012. **380**(9849): p. 1231-1240.
16. Alexandrov, A.V., et al., *Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke*. N Engl J Med, 2004. **351**(21): p. 2170-8.
17. Rha, J.H. and J.L. Saver, *The impact of recanalization on ischemic stroke outcome: a meta-analysis*. Stroke, 2007. **38**(3): p. 967-73.
18. Wunderlich, M.T., et al., *Recanalization after intravenous thrombolysis: does a recanalization time window exist?* Neurology, 2007. **68**(17): p. 1364-8.
19. Nogueira, R.G., L.H. Schwamm, and J.A. Hirsch, *Endovascular Approaches to Acute Stroke, Part 1: Drugs, Devices, and Data*. AJNR Am J Neuroradiol, 2009.
20. Nogueira, R.G., et al., *Endovascular approaches to acute stroke, part 2: a comprehensive review of studies and trials*. AJNR Am J Neuroradiol, 2009. **30**(5): p. 859-75.
21. Furlan, A.J., *Clot retrieval for stroke should be restricted to clinical trials: no*. Stroke, 2010. **41**(1): p. 194-5.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

22. Hernandez-Perez, *Natural History of Acute Stroke due to Occlusion of the Middle Cerebral Artery and Intracranial Internal Carotid Artery*, in *Journal of Neuroimaging*, e. al, Editor. 2013: (In press at time of this writing).
23. Gonzalez, R., et al. (2012) *Improved Outcome Prediction Using CT Angiography in Addition to Standard Ischemic Stroke Assessment: Results from the STOPStroke Study*. PLoS ONE 7, e30352 DOI: 10.1371/journal.pone.0030352
24. Janardhan V, G.R., Chen SH, et al. *Preliminary Results from the FIRST Trial: Natural History of Acute Stroke from Large Vessel Occlusion*. in *International Stroke Conference*. 2013. Honolulu, HI: Stroke. 44:A194.
25. Furlan, A., et al., *Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial*. *Prolyse in Acute Cerebral Thromboembolism*. Jama, 1999. **282**(21): p. 2003-11.
26. Ogawa, A., et al., *Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan*. *Stroke*, 2007. **38**(10): p. 2633-9.
27. Furlan, *Personal Communication to Raul Nogueira re: ProAct II - M1 subgroup good outcomes.*, R. Nogueira, Editor. 2013.
28. Nogueira, R.G., et al. *Preliminary Data for the DAWN Trial (DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention): Results of Imaging-Based Endovascular Therapy for Proximal Anterior Circulation Occlusions beyond 8 Hours from Last Seen Well in 237 Stroke Patients*. in *Society of Neurointerventional Surgery (SNIS) 6th Annual Meeting*. 2009. Boca Raton, Florida.
29. Jauch EC, S.J., Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H *Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association*. *Stroke*, 2013.
30. Kleindorfer, D., et al., *Emergency Department Arrival Times after Acute Ischemic Stroke During the 1990s*. *Neurocritical Care*, 2007. **7**(1): p. 31-35.
31. Fink, J.N., et al., *The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI*. *Stroke*, 2002. **33**(4): p. 988-93.
32. Silva, G.S., et al., *Wake-up stroke: clinical and neuroimaging characteristics*. *Cerebrovasc Dis*, 2010. **29**(4): p. 336-42.
33. Todo, K., et al., *Early CT findings in unknown-onset and wake-up strokes*. *Cerebrovasc Dis*, 2006. **21**(5-6): p. 367-71.
34. Adams, H.P., Jr., et al., *Treating patients with 'wake-up' stroke: the experience of the AbESTT-II trial*. *Stroke*, 2008. **39**(12): p. 3277-82.
35. Barreto, A.D., et al., *Thrombolytic therapy for patients who wake-up with stroke*. *Stroke*, 2009. **40**(3): p. 827-32.
36. Cho, A.H., et al., *Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke. A preliminary report*. *Cerebrovasc Dis*, 2008. **25**(6): p. 572-9.
37. Copen, W.A., et al., *Existence of the diffusion-perfusion mismatch within 24 hours after onset of acute stroke: dependence on proximal arterial occlusion*. *Radiology*, 2009. **250**(3): p. 878-86.
38. Jovin, T.G., et al., *Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients*. *Stroke*, 2011. **42**(8): p. 2206-11.
39. Thomalla, G., et al., *Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials*. *Stroke*, 2006. **37**(3): p. 852-8.
40. Kohrmann, M., et al., *MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: a cohort study*. *Lancet Neurol*, 2006. **5**(8): p. 661-7.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

41. Schellinger, P.D., et al., *MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients.* Stroke, 2007. **38**(10): p. 2640-5.
42. Janjua, N., et al., *Late endovascular revascularization in acute ischemic stroke based on clinical-diffusion mismatch.* AJNR Am J Neuroradiol, 2009. **30**(5): p. 1024-7.
43. Natarajan, S.K., et al., *Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes.* Stroke, 2009. **40**(10): p. 3269-74.
44. Zaidi, S., et al. *Intra-arterial Treatment for Acute Anterior Circulation Ischemic Strokes Due to Large Vessel Occlusion Beyond 8 Hours – Preliminary Results.* in European Stroke Conference. 2008. Nice, France.
45. Rai, A.T., et al., *Endovascular therapy yields significantly superior outcomes for large vessel occlusions compared with intravenous thrombolysis: is it time to randomize?* Journal of NeuroInterventional Surgery, 2012.
46. Rai, A.T., et al., *Pre-intervention triage incorporating perfusion imaging improves outcomes in patients undergoing endovascular stroke therapy: a comparison with the device trials.* Journal of NeuroInterventional Surgery, 2013. **5**(2): p. 121-127.
47. Turk, A.S., et al., *Utilization of CT perfusion patient selection for mechanical thrombectomy irrespective of time: a comparison of functional outcomes and complications.* Journal of NeuroInterventional Surgery, 2012.
48. Rivero-Arias, O., et al., *Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome.* Medical decision making, 2010. **30**(3): p. 341-354.
49. Hong, K.-S. and J.L. Saver, *Quantifying the Value of Stroke Disability Outcomes WHO Global Burden of Disease Project Disability Weights for Each Level of the Modified Rankin Scale.* Stroke, 2009. **40**(12): p. 3828-3833.
50. Castano, C., et al., *Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation: a pilot study.* Stroke, 2010. **41**(8): p. 1836-40.
51. Roth, C., et al., *Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions.* Stroke, 2010. **41**(11): p. 2559-2567.
52. Mpotseris, A., et al., *Mechanical thrombectomy in severe acute stroke: preliminary results of the Solitaire stent.* Journal of Neurology, Neurosurgery & Psychiatry, 2012. **83**(1): p. 117-118.
53. Galimianis, A., et al., *Endovascular therapy of 623 patients with anterior circulation stroke.* Stroke, 2012. **43**(4): p. 1052-1057.
54. Flint, A.C., et al., *Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials.* Stroke, 2007. **38**(4): p. 1274-80.
55. Tarr, R., et al., *The POST Trial: Initial Post-Market Experience of the Penumbra System: Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke in the United States and Europe.* Journal of NeuroInterventional Surgery, 2010. **2**(): p. 341-344.
56. Dávalos, A., et al., *Retrospective multicenter study of Solitaire FR for revascularization in the treatment of acute ischemic stroke.* Stroke, 2012. **43**(10): p. 2699-2705.
57. Wahlgren, N., et al. *Final Results From The Trevo Study (Thrombectomy REvascularization of large Vessel Occlusions in acute ischemic stroke).* in International Stroke Conference. 2012. New Orleans, LA.
58. Broderick, J.P., et al., *Endovascular therapy after intravenous t-pa versus t-pa alone for stroke.* New England Journal of Medicine, 2013. **368**(10): p. 893-903.
59. Kidwell, C.S., et al., *A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke.* New England Journal of Medicine, 2013. **368**(10): p. 914-923.
60. Ciccone, A., et al., *Endovascular Treatment for Acute Ischemic Stroke.* New England Journal of Medicine, 2013. **368**(10): p. 904-913.
61. Albuquerque, F.C., et al., *The tribulations of stroke trials.* Journal of NeuroInterventional Surgery, 2013. **5**(3): p. 181-183.
62. SIR. *Society of Interventional Radiologists letter re: Use of Thrombectomy Devies for the Emergent Treatment of Acute Ischemic Stroke.* 2013; Available from: <http://www.sirweb.org/misc/SIRLetter%20CTAF%20STROKE%20Mar2013.pdf>.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

63. Wisco, *Addition of MRI for Patient Selection in Intra-arterial Stroke Therapy Leads to Better Clinical Outcomes, a Pre-Post Study in International Stroke Conference Oral Abstracts; A161.* 2012.
64. Kidwell, C.S., J.R. Alger, and J.L. Saver, *Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging.* Stroke, 2003. **34**(11): p. 2729-35.
65. Donnan, G.A., et al., *Penumbbral selection of patients for trials of acute stroke therapy.* Lancet Neurol, 2009. **8**(3): p. 261-9.
66. Saver, J.L., *Time is brain--quantified.* Stroke, 2006. **37**(1): p. 263-6.
67. Leiva-Salinas, C., et al., *Tissue at risk in acute stroke patients treated beyond 8 h after symptom onset.* Neuroradiology, 2013: p. 1-6.
68. Abou-Chebl, A., *Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients.* Stroke, 2010. **41**(9): p. 1996-2000.
69. Wechsler, L.R., et al., *Factors influencing outcome and treatment effect in PROACT II.* Stroke, 2003. **34**(5): p. 1224-9.
70. Khatri, P., et al., *Good clinical outcome after ischemic stroke with successful revascularization is time-dependent.* Neurology, 2009. **73**(13): p. 1066-72.
71. Nogueira, R.G., et al., *Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials.* Stroke, 2009. **40**(12): p. 3777-83.
72. Nogueira, R.G., et al. *Endovascular Therapy for AIS Due to Proximal Arterial Occlusion Treated Beyond 8 Hours from Time Last Seen Well: A Subset Analysis of the Merci Registry.* in Eighth Society of NeuroInterventional Surgery (SNIS) Annual Meeting. 2011. Colorado Springs, Colorado, USA.
73. Jung, S., et al., *Safety of endovascular treatment beyond the 6-h time window in 205 patients.* European Journal of Neurology, 2013.
74. Nogueira, R.G., et al., *Neither Time to Treatment Nor the Use of Adjunctive Intra-arterial Thrombolytics Increase the Risk for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of CT Perfusion or MRI-selected Stroke Patients Treated at Late Time Windows: Analysis of the Pre-DAWN Dataset.* ISC:A93. 2010: Austin, Tx.
75. STAIR. *Stroke Treatment Academic Industry Roundtable. March 9-10, 2013. Washington D.C. "Accelerating the Evolution of Stroke Therapy".* In Press. 2013.
76. Wolpert, S.M., et al., *Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator.* The rt-PA Acute Stroke Study Group. AJNR Am J Neuroradiol, 1993. **14**(1): p. 3-13.
77. Shi, Z.-S., et al., *Endovascular Thrombectomy for Acute Ischemic Stroke in Failed Intravenous Tissue Plasminogen Activator Versus Non-Intravenous Tissue Plasminogen Activator Patients Revascularization and Outcomes Stratified by the Site of Arterial Occlusions.* Stroke, 2010. **41**(6): p. 1185-1192.
78. Davalos, A., et al., *The clinical-DWI mismatch: a new diagnostic approach to the brain tissue at risk of infarction.* Neurology, 2004. **62**(12): p. 2187-92.
79. Ebinger, M., et al., *Clinical-diffusion mismatch and benefit from thrombolysis 3 to 6 hours after acute stroke.* Stroke, 2009. **40**(7): p. 2572-4.
80. Lansberg, M.G., et al., *Evaluation of the clinical-diffusion and perfusion-diffusion mismatch models in DEFUSE.* Stroke, 2007. **38**(6): p. 1826-30.
81. Nogueira, R.G., et al., *Clinical-Diffusion Mismatch Better Discriminates Infarct Growth than MTT-DWI Mismatch in Patients with MCA-M1 Occlusion and Limited Infarct Core.* AJNR, 2013 (Submitted March).
82. Prosser, J., et al., *Clinical-diffusion mismatch predicts the putative penumbra with high specificity.* Stroke, 2005. **36**(8): p. 1700-4.
83. Albers, G.W., et al., *Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study.* Ann Neurol, 2006. **60**(5): p. 508-17.
84. Lansberg, M.G., et al., *Results of DEFUSE 2: Imaging Endpoints.* Stroke.2012;43:A52, 2012.
85. Mishra, N.K., et al., *Mismatch-based delayed thrombolysis: a meta-analysis.* Stroke, 2010. **41**(1): p. e25-33.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

86. Dani, K.A., et al., *Systematic review of perfusion imaging with computed tomography and magnetic resonance in acute ischemic stroke: heterogeneity of acquisition and postprocessing parameters: a translational medicine research collaboration multicentre acute stroke imaging study.* Stroke, 2012. **43**(2): p. 563-6.
87. Goyal, M., B.K. Menon, and C.P. Derdeyn, *Perfusion Imaging in Acute Ischemic Stroke: Let Us Improve the Science before Changing Clinical Practice.* Radiology, 2013. **266**(1): p. 16-21.
88. Jovin, T.G., et al., *The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion.* Stroke, 2003. **34**(10): p. 2426-33.
89. Nogueira, R.G., et al., *Infarct Volume Thresholds for Prediction of Independent Functional Outcomes after Acute Ischemic Stroke.* Stroke 2012. **43**: p. A4030.
90. Lansberg, M.G., et al., *MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study.* The Lancet Neurology, 2012.
91. Zaidi, S.F., et al., *Final infarct volume is a stronger predictor of outcome than recanalization in patients with proximal middle cerebral artery occlusion treated with endovascular therapy.* Stroke, 2012. **43**(12): p. 3238-3244.
92. Furlan, *Personal Communication to Tudor Jovin re: ProAct II - Outcomes by Occlusion Location and NIHSS.* T. Jovin, Editor. 2013.
93. Fischer, U., et al., *NIHSS score and arteriographic findings in acute ischemic stroke.* Stroke, 2005. **36**(10): p. 2121-5.
94. Lewandowski, C.A., et al., *Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial.* Stroke, 1999. **30**(12): p. 2598-605.
95. DeGraba, T.J., et al., *Progression in acute stroke value of the initial NIH Stroke Scale score on patient stratification in future trials.* Stroke, 1999. **30**(6): p. 1208-1212.
96. Ringleb, P.A., et al., *Thrombolytic therapy for acute ischaemic stroke in octogenarians: selection by magnetic resonance imaging improves safety but does not improve outcome.* Journal of Neurology, Neurosurgery & Psychiatry, 2007. **78**(7): p. 690-693.
97. Mishra, N.K., et al., *Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA).* Stroke, 2010. **41**(12): p. 2840-8.
98. Bath, P.M., et al., *Statistical analysis of the primary outcome in acute stroke trials.* Stroke, 2012. **43**(4): p. 1171-1178.
99. Fisher, M., et al., *Stroke Therapy Academic Industry Roundtable IV. Enhancing the development and approval of acute stroke therapies: stroke therapy academic industry roundtable.* Stroke, 2005. **36**(8): p. 1808-1813.
100. Krams, M., K.R. Lees, and D.A. Berry, *The Past Is the Future Innovative Designs in Acute Stroke Therapy Trials.* Stroke, 2005. **36**(6): p. 1341-1347.
101. Shuaib, A., et al., *Partial Aortic Occlusion for Cerebral Perfusion Augmentation Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke Trial.* Stroke, 2011. **42**(6): p. 1680-1690.
102. Kaufmann, e.a., *Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients.* Radiology, 2007. **243**: p. 812-819.
103. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.* N Engl J Med, 2008. **359**(13): p. 1317-29.
104. Chaisinanunkul , N., et al. *Adopting a Patient-Centered Approach to Primary Outcome Analysis of Acute Stroke Trials Using a Utility-Weighted Modified Rankin Scale.* Stroke. 2015. **46**:2238-2243

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Abbreviation	Full Term
CTP	Computerized Tomography Perfusion
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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Abbreviation	Full Term
ICA	Internal Carotid Artery
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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Abbreviation	Full Term
MCA	Middle Cerebral Artery
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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Abbreviation	Full Term
SAH	Subarachnoid Hemorrhage
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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 uninvolvled 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 uninvolvled 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 for a pre-existing condition or a condition required by the protocol, without serious deterioration in health is not considered serious.

Stroke: An acute neurological event with focal symptoms and signs lasting \geq 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 \geq 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 ($\geq 2/3$) 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 uninvolves other bed of the same vessel or the opposite cerebral artery

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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 $\geq 50\%$ 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Appendix D. Informed Consent Form Template [attached]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AB

Appendix F. Adaptive Design Plan [attached]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Sponsor:	Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515
Study Responsibility:	Christine Yang Toruno Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: christine.toruno@stryker.com Tel: (510) 413-2841 e-Fax: (855) 328-1403
Coordinating Principal Investigators:	Tudor G. Jovin, MD Associate Professor of Neurology and Neurosurgery Director UPMC Stroke Institute UPMC Presbyterian, Fourth Floor, Suite C400 200 Lothrop Street Pittsburgh, PA 15213 Email: jovitg@upmc.edu Tel: (412) 647-4999 or (412) 647-3030 Fax: (412) 647-8445 Raul Nogueira, MD Director of Neuroendovascular Service Marcus Stroke & Neuroscience Center Grady Memorial Hospital Associate Professor of Neurology, Neurosurgery and Radiology Emory University School of Medicine Emory Faculty Office Building 80 Jesse Hill Drive SE Room# 398 Atlanta, GA 30303 Email: raul.g.nogueira@emory.edu Tel: (404) 616-4013 Fax: (404) 659-0849
Study Centers:	A current list of sites will be maintained in the Sponsor's Study Files.
Date / Version:	24 Apr 2014 Rev: AA
Date(s) of Amendment(s):	14 Sep 2015 Rev: AB; 28 April 2016 Rev: AC; 26 Jan 2017 Rev: AD

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. Do not copy or distribute without written permission.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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	<ol style="list-style-type: none">1. Proportion of subjects with a good functional outcome at 90 days, defined as mRS 0-22. 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 13. 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. <u>Treatment Arm Only:</u> Analysis of vessel reperfusion rates (percentages) post device and post procedure, by angiography core lab measurement of modified TICI $\geq 2b$

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Primary Safety Outcome	<u>Both Arms:</u> <ol style="list-style-type: none"> 1. Incidence of stroke-related mortality at 90 days 																
Secondary Safety Outcomes	<u>Both Arms:</u> <ol style="list-style-type: none"> 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. <u>Treatment Arm:</u> <ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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 (<i>in vivo</i> breakage) g. any other complications adjudicated by the CEC to be related to the procedure 																
Efficacy Parameter	<p>Modified Rankin Scale score at 90 days:</p> <p>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</p> <p>Note: For purposes of primary efficacy weighted mRS analysis each mRS category will be assigned a numerical value representing its clinical utility, as follows:</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <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>	mRS	0	1	2	3	4	5	6	Weight	10	9.1	7.6	6.5	3.3	0	0
mRS	0	1	2	3	4	5	6										
Weight	10	9.1	7.6	6.5	3.3	0	0										
Randomization	<p>Subjects will be randomized 1:1 to Trevo thrombectomy plus medical management or medical management alone.</p> <p><u>Stratification will occur by:</u> 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).</p> <p>After randomization, no crossover is permitted.</p> <p>Enrollment in this study is defined as the moment when the randomization process is completed and the subject is assigned to a study arm.</p>																

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Study Duration	<ul style="list-style-type: none"> • Enrollment: approximately 36 months • Subject participation: 90 days (\pm 14) • Total Study Duration: approximately 39 months (+/- 9 months)
Follow-Up Schedule	<p>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.</p> <ol style="list-style-type: none"> 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 <u>blinded</u> mRS (Optional repeat MRI T2/Flair or CT, if MR is contraindicated, may be performed to assess infarct volume) 3. Day 30 (\pm 14): NIHSS and blinded mRS 4. Day 90 (\pm 14): NIHSS and blinded mRS
General Inclusion Criteria	<ol style="list-style-type: none"> 1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, <u>and</u> subject belongs to one of the following subgroups: <ol style="list-style-type: none"> 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 \geq18 3. Baseline NIHSS \geq10 (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* <p>* 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.)</p>
General Inclusion Criteria (additional information)	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> a. 0-<21 cc core infarct and NIHSS \geq 10 (and age \geq 80 years old) b. 0-<31 cc core infarct and NIHSS \geq 10 (and age < 80 years old) c. 31 cc to <51 cc core infarct and NIHSS \geq 20 (and age < 80 years old)

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

General Exclusion Criteria	<ol style="list-style-type: none">1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history2. Rapid improvement in neurological status to an NIHSS <10 or evidence of vessel recanalization prior to randomization3. 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 assessment5. 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/uL8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L9. 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 levels10. 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 days12. History of severe allergy (more than rash) to contrast medium13. 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 enrolled14. Female who is pregnant or lactating at time of admission15. Current participation in another investigational drug or device study16. Presumed septic embolus, or suspicion of bacterial endocarditis17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. Evidence of intracranial hemorrhage on CT/MRI2. 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/deployment4. Suspected cerebral vasculitis based on medical history and CTA/MRA5. Suspected aortic dissection based on medical history and CTA/MRA6. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

	<ul style="list-style-type: none"> 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	<p>Treatment Arm:</p> <ol style="list-style-type: none"> 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. <p>Medical Management Arm:</p> <ol style="list-style-type: none"> 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. <p>Both Arms:</p> <ol style="list-style-type: none"> 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 .

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

1	Introduction and Rationale	13
1.1	Incidence and Burden of Stroke	13
1.2	Current Treatment Options	13
1.3	Unmet Need in Acute Ischemic Stroke	13
1.4	Purpose of Study	15
2	Study Device.....	15
2.1	Study Device Description	15
2.2	Study Device Labeling	17
3	Study Objective	18
3.1	Primary Objective	18
3.2	Secondary Objectives.....	18
4	Study Endpoints and Safety Outcomes	18
4.1	Primary Endpoint	18
4.2	Secondary Endpoints.....	19
4.3	Primary Safety Outcome	19
4.4	Secondary Safety Outcomes	19
5	Study Design	20
5.1	Overview	20
5.2	Justification for the Study Design	22
	<i>5.2.1Justification for Expansion of Time Window</i>	<i>23</i>
	<i>5.2.2Justification for Inclusion of Wake up and Unclear Onset Strokes</i>	<i>27</i>
	<i>5.2.3Justification for Inclusion of IV tPA Failures.....</i>	<i>27</i>
	<i>5.2.4Justification for Non Reliance on Penumbra Imaging.....</i>	<i>28</i>
	<i>5.2.5Justification for Use of Clinical Imaging Mismatch Criteria.....</i>	<i>29</i>
	<i>5.2.6Justification for Use of Standardized Core Infarct Imaging Software</i>	<i>31</i>
	<i>5.2.7Justification for Use of Weighted mRS as Primary Endpoint.....</i>	<i>31</i>
	<i>5.2.8Justification for Use of Adaptive Design</i>	<i>32</i>
5.3	Method of Assigning Subjects to Treatments	33
5.4	Blinding and Breaking the Blind.....	33
6	Study Population	34
6.1	Inclusion Criteria	34

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

6.2	Exclusion Criteria	34
6.3	Withdrawal and Replacement of Subjects	36
6.4	Enrollment Controls	36
7	Study Procedures.....	36
7.1	Written Informed Consent.....	36
7.2	Prior to Randomization	37
7.3	Angiography Procedure (Treatment arm only)	40
	<i>7.3.1Diagnostic Angiography</i>	40
	<i>7.3.2Unexpected Diagnostic Angiography Findings</i>	41
7.4	Trevo Thrombectomy Procedure (Treatment arm only)	43
7.5	End of the Trevo Thrombectomy Procedure (Treatment arm only).....	45
7.6	24 (-6 / +24) Hours post Randomization.....	46
7.7	Concomitant Medications and Management.....	46
	<i>7.7.1Blood pressure management</i>	47
	<i>7.7.2Glucose management</i>	48
7.8	Day 5-7 / Discharge	48
7.9	Post Discharge Follow-up.....	48
	<i>7.9.1Day 30 (± 14)</i>	49
	<i>7.9.2Day 90 (± 30)</i>	49
8	Statistical Methods	50
8.1	Sample Size Estimate and Justification.....	50
8.2	Control of Systematic Error/Bias	50
8.3	Eligibility of Subjects, Exclusions, and Missing Data	51
8.4	Population Definitions	51
8.5	Analysis Populations.....	52
8.6	Interim Analysis.....	52
	<i>8.6.1Interim Monitoring for Early Futility</i>	53
	<i>8.6.2Enrichment</i>	53
	<i>8.6.3Interim Monitoring for Expected Success</i>	53
	<i>8.6.4Longitudinal Model</i>	54
8.7	Statistical Analysis.....	54
	<i>8.7.1Baseline Comparability</i>	55
	<i>8.7.2Pooling Across Institutions</i>	55

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

8.7.3 <i>Other Pre-planned Analyses</i>	55
8.7.4 <i>Health Economics Information</i>	55
9 Data Management	56
9.1 Data Collection and Processing	56
10 Monitoring Procedures	56
10.1 Auditing	56
10.2 Investigational Device Accountability	57
11 Adverse Events	57
11.1 Adverse Event Definitions and Classification.....	57
11.2 Adverse Events Reporting Requirements	59
11.3 Device Failures, Malfunctions, and Product Nonconformities	60
11.4 Reporting to Regulatory Authorities / IRBs / ECs / Investigators	60
12 Risk Benefit Analysis.....	61
12.1 CT/MR Imaging	62
12.2 Investigational procedure (Treatment arm only).....	62
<i>12.2.1 ..Diagnostic Angiography</i>	62
<i>12.2.2 ..Trevo Thrombectomy</i>	63
12.3 Risk Minimization.....	64
13 Study Committees and Core Labs	64
13.1 Steering Committee.....	64
13.2 Safety Monitoring Committees	65
<i>13.2.1 ..Clinical Events Committee (CEC)</i>	65
<i>13.2.2 ..Data Monitoring Committee (DMC)</i>	66
13.3 Imaging Core Labs.....	67
<i>13.3.1 ..Angiographic Core Lab</i>	68
<i>13.3.2 ..CT/MR Core Lab</i>	68
14 Ethical Considerations	69
14.1 Compliance with Good Clinical Practices (GCP)	69
14.2 Institutional Review Board/ Ethics Committee	69
14.3 Written Informed Consent Form	70
14.4 Amending the Protocol	70
14.5 Protocol Adherence	70
15 Study Administration.....	71

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

15.1	Pre-Study Documentation Requirements	71
15.2	Record Retention	71
15.3	Criteria for Terminating Study.....	71
15.4	Criteria for Suspending/Terminating a Study Site	71
16	References	73
17	Appendices	78
Appendix A.	Abbreviations.....	78
Appendix B.	Definitions	83
Appendix C.	Angiographic Core Lab Scales	87
Appendix D.	Informed Consent Form Template [attached]	89
Appendix E.	Sample Instructions for Use (IFU) [attached]	90
Appendix F.	Adaptive Design Plan [attached]	91

List of Figures

Figure 1.	Trevo Retrievers	17
Figure 2.	DAWN™ Trial Flow Chart	21

List of Tables

Table 1.	Key Dimensions of Trevo Family Retrievers	16
Table 2.	Zaidi - Anterior LVOs treated \leq 8 hrs and $>$ 8 hrs after TLSW.....	24
Table 3.	Merci Registry - Anterior LVOs treated \leq 8 hr and $>$ 8 hr after TLSW	25
Table 4.	Pre-DAWN Cohort vs. PROACT II Treatment and Control Arm.....	26
Table 5.	DAWN™ Trial Time and Events Schedule.....	39
Table 6.	Distribution of mRS outcomes for the control arm in the simulations	50
Table 7.	Intracranial Hemorrhage Types	69

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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, Stentriever™ 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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 unwitnessed 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

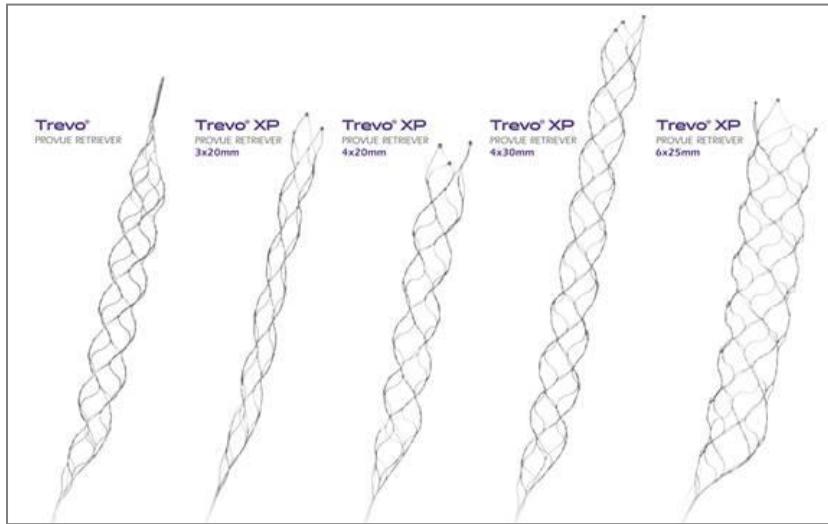
Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- 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).

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 $\geq 2b$.

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

[Remainder of page is intentionally blank.]

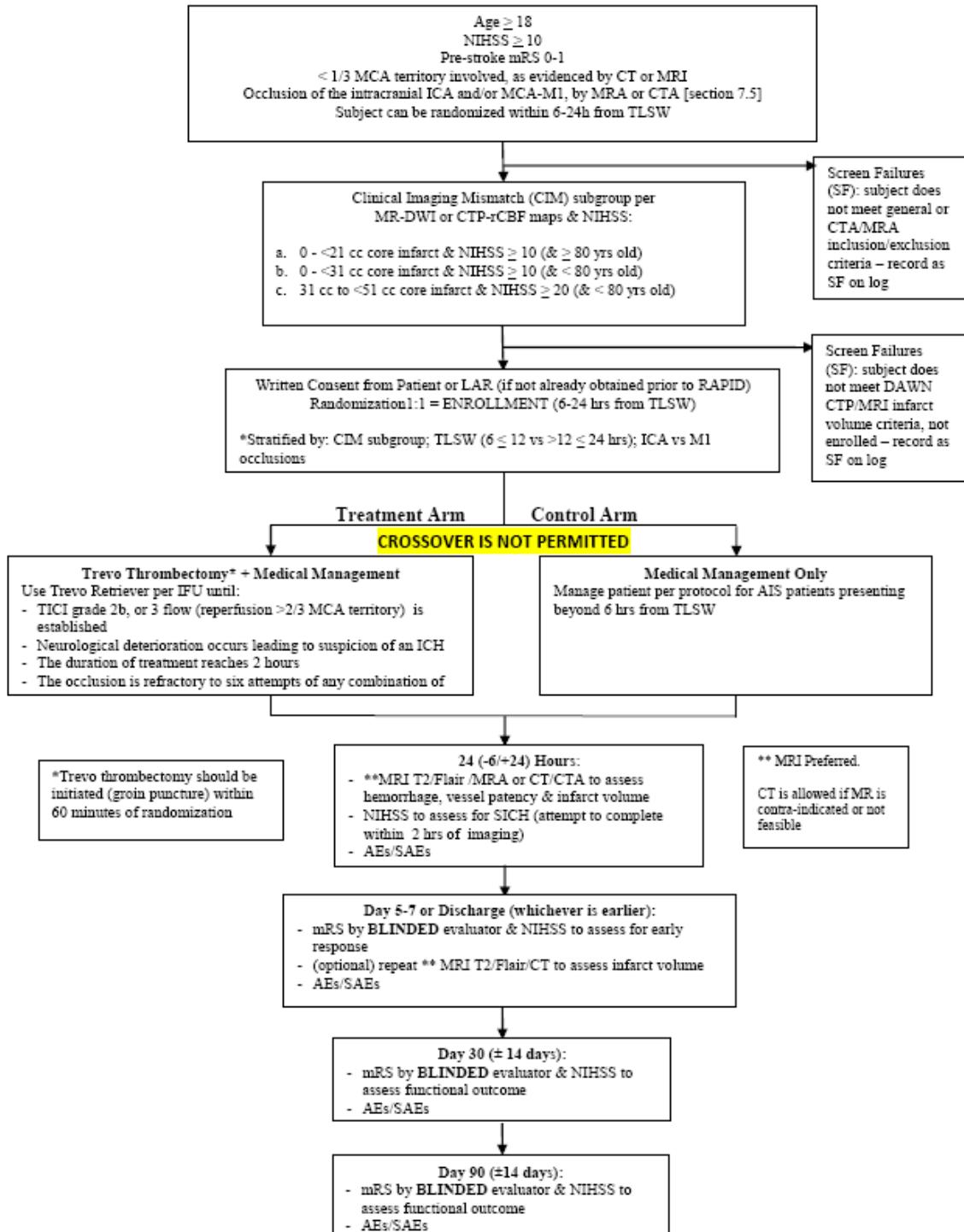
Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Figure 2. DAWN™ Trial Flow Chart



STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 Stentriever™ 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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: ≤ 8 hr (n=123) and >8 hr (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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 TSLW

	$\leq 8\text{hr}$ (N=123)	$> 8\text{hr}$ (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 TSLW. [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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Table 3. Merci Registry - Anterior LVOs treated \leq 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 TSW and SICH. [74]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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) TSWL 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 TSWL 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 \pm SD	64 \pm 16	64 \pm 14	64 \pm 14
Median Baseline NIHSS (Min-Max)	17 (10 - 29)	17 (5 - 27)	17 (4 - 28)
Female	54%	42%	39%
TSWL 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	0%	35%	37%
MCA-M1	54%	61%	63%
ICA-T	22%	0%	0%
Tandem ICA/MCA	17%	0%	0%
Tandem ICA/ICA-T	7%	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 TSWL in appropriately selected subjects.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 infarcted 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 neurothrombectomy, including infarct core size, presence of salvageable penumbra, etc. A

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 \leq 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 (\pm 14) and Day 90 (\pm 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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

6 Study Population

6.1 Inclusion Criteria

General Inclusion Criteria	<ol style="list-style-type: none">1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, <u>and</u> subject belongs to one of the following subgroups:<ol style="list-style-type: none">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 administration2. Age ≥ 183. 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 well5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1)6. Anticipated life expectancy of at least 6 months7. Subject willing/able to return for protocol required follow up visits8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form* <p>* 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.)</p>
General Inclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. $< 1/3$ MCA territory involved, as evidenced by CT or MRI2. Occlusion of the intracranial ICA and/or MCA-M1 as evidenced by MRA or CTA3. Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps:<ol style="list-style-type: none">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 <u>≤ 51</u> cc core infarct and NIHSS ≥ 20 (and age < 80 years old)

6.2 Exclusion Criteria

General Exclusion Criteria	<ol style="list-style-type: none">1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history2. Rapid improvement in neurological status to an NIHSS < 10 or evidence of vessel recanalization prior to randomization3. 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 assessment5. Baseline blood glucose of < 50 mg/dL (2.78 mmol) or > 400 mg/dL (22.20 mmol)
----------------------------	--

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

	<ol style="list-style-type: none">6. Baseline hemoglobin counts of <7 mmol/L (11.28 g/dL)7. Baseline platelet count < 50,000/uL8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L9. 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 levels10. 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 days12. History of severe allergy (more than rash) to contrast medium13. 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 enrolled14. Female who is pregnant or lactating at time of admission15. Current participation in another investigational drug or device study16. Presumed septic embolus, or suspicion of bacterial endocarditis17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Exclusion Criteria (additional information)	<ol style="list-style-type: none">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	<ol style="list-style-type: none">1. Evidence of intracranial hemorrhage on CT/MRI2. 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/deployment4. Suspected cerebral vasculitis based on medical history and CTA/MRA5. Suspected aortic dissection based on medical history and CTA/MRA6. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device7. 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 territories8. Significant mass effect with midline shift as confirmed on CT/MRI9. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 (\pm 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

(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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- 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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- “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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

[Remainder of page is intentionally blank.]

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 (\pm 14) follow-up assessments. Requirements of each follow-up evaluation are detailed below.

7.9.1 **Day 30 (\pm 14)**

At Day 30 (\pm 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 \pm 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 (\pm 14)**

At Day 90 (\pm 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 \pm 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 \geq 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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. <i>Note 1:</i> This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. <i>Note 2:</i> This definition includes any event that is a result of a user error.	ISO 14155-1

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Term	Definition	Reference
Serious adverse event (SAE)	<p>An adverse event that:</p> <ul style="list-style-type: none">• 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)	<p>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.</p>	ISO 14155-1
Unanticipated Adverse Device Effect (UADE)	<p>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.</p>	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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 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:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- 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 thrombectomy 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- 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,

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Core infarct 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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**.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

16 References

1. CDC. *Stroke Facts*. 2013; Available from: <http://www.cdc.gov/stroke.facts.htm>.
2. Roger, V.L., et al., *Heart Disease and Stroke Statistics—2012 Update A Report From the American Heart Association*. Circulation, 2012. **125**(1): p. e2-e220.
3. Smith, W.S., et al., *Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia*. Neurocrit Care, 2006. **4**(1): p. 14-7.
4. Heidenreich, P.A., et al., *Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association*. Circulation, 2011. **123**(8): p. 933-944.
5. Katzen, I.L., et al., *Utilization of intravenous tissue plasminogen activator for acute ischemic stroke*. Arch Neurol, 2004. **61**(3): p. 346-50.
6. Hacke, W., et al., *Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials*. Lancet, 2004. **363**(9411): p. 768-74.
7. Marler, J.R., et al., *Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study*. Neurology, 2000. **55**(11): p. 1649-55.
8. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke*. New England Journal of Medicine, 2008. **359**(13): p. 1317-1329.
9. Bhatia, R., et al., *Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action*. Stroke, 2010. **41**(10): p. 2254-8.
10. Riedel, C.H., et al., *The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length*. Stroke, 2011. **42**(6): p. 1775-7.
11. Smith, W.S., et al., *Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial*. Stroke, 2008. **39**(4): p. 1205-12.
12. Smith, W.S., et al., *Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial*. Stroke, 2005. **36**(7): p. 1432-8.
13. Clark, W., et al., *The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease*. Stroke, 2009. **40**(8): p. 2761-2768.
14. Saver, J.L., et al., *Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial*. The Lancet, 2012. **380**(9849): p. 1241-1249.
15. Nogueira, R.G., et al., *Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial*. The Lancet, 2012. **380**(9849): p. 1231-1240.
16. Alexandrov, A.V., et al., *Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke*. N Engl J Med, 2004. **351**(21): p. 2170-8.
17. Rha, J.H. and J.L. Saver, *The impact of recanalization on ischemic stroke outcome: a meta-analysis*. Stroke, 2007. **38**(3): p. 967-73.
18. Wunderlich, M.T., et al., *Recanalization after intravenous thrombolysis: does a recanalization time window exist?* Neurology, 2007. **68**(17): p. 1364-8.
19. Nogueira, R.G., L.H. Schwamm, and J.A. Hirsch, *Endovascular Approaches to Acute Stroke, Part 1: Drugs, Devices, and Data*. AJNR Am J Neuroradiol, 2009.
20. Nogueira, R.G., et al., *Endovascular approaches to acute stroke, part 2: a comprehensive review of studies and trials*. AJNR Am J Neuroradiol, 2009. **30**(5): p. 859-75.
21. Furlan, A.J., *Clot retrieval for stroke should be restricted to clinical trials: no.* Stroke, 2010. **41**(1): p. 194-5.
22. Hernandez-Perez, *Natural History of Acute Stroke due to Occlusion of the Middle Cerebral Artery and Intracranial Internal Carotid Artery*, in *Journal of Neuroimaging*, e. al, Editor. 2013: (In press at time of this writing).

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

23. Gonzalez, R., et al. (2012) *Improved Outcome Prediction Using CT Angiography in Addition to Standard Ischemic Stroke Assessment: Results from the STOPStroke Study*. PLoS ONE 7, e30352 DOI: 10.1371/journal.pone.0030352
24. Janardhan V, G.R., Chen SH, et al. *Preliminary Results from the FIRST Trial: Natural History of Acute Stroke from Large Vessel Occlusion*. in *International Stroke Conference*. 2013. Honolulu, HI: Stroke. 44:A194.
25. Furlan, A., et al., *Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism*. Jama, 1999. **282**(21): p. 2003-11.
26. Ogawa, A., et al., *Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan*. Stroke, 2007. **38**(10): p. 2633-9.
27. Furlan, *Personal Communication to Raul Nogueira re: ProAct II - M1 subgroup good outcomes*, R. Nogueira, Editor. 2013.
28. Nogueira, R.G., et al. *Preliminary Data for the DAWN Trial (DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention): Results of Imaging-Based Endovascular Therapy for Proximal Anterior Circulation Occlusions beyond 8 Hours from Last Seen Well in 237 Stroke Patients*. in *Society of Neurointerventional Surgery (SNIS) 6th Annual Meeting*. 2009. Boca Raton, Florida.
29. Jauch EC, S.J., Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H *Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association*. Stroke, 2013.
30. Kleindorfer, D., et al., *Emergency Department Arrival Times after Acute Ischemic Stroke During the 1990s*. Neurocritical Care, 2007. **7**(1): p. 31-35.
31. Fink, J.N., et al., *The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI*. Stroke, 2002. **33**(4): p. 988-93.
32. Silva, G.S., et al., *Wake-up stroke: clinical and neuroimaging characteristics*. Cerebrovasc Dis, 2010. **29**(4): p. 336-42.
33. Todo, K., et al., *Early CT findings in unknown-onset and wake-up strokes*. Cerebrovasc Dis, 2006. **21**(5-6): p. 367-71.
34. Adams, H.P., Jr., et al., *Treating patients with 'wake-up' stroke: the experience of the AbESTT-II trial*. Stroke, 2008. **39**(12): p. 3277-82.
35. Barreto, A.D., et al., *Thrombolytic therapy for patients who wake-up with stroke*. Stroke, 2009. **40**(3): p. 827-32.
36. Cho, A.H., et al., *Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke. A preliminary report*. Cerebrovasc Dis, 2008. **25**(6): p. 572-9.
37. Copen, W.A., et al., *Existence of the diffusion-perfusion mismatch within 24 hours after onset of acute stroke: dependence on proximal arterial occlusion*. Radiology, 2009. **250**(3): p. 878-86.
38. Jovin, T.G., et al., *Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients*. Stroke, 2011. **42**(8): p. 2206-11.
39. Thomalla, G., et al., *Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials*. Stroke, 2006. **37**(3): p. 852-8.
40. Kohrmann, M., et al., *MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: a cohort study*. Lancet Neurol, 2006. **5**(8): p. 661-7.
41. Schellinger, P.D., et al., *MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients*. Stroke, 2007. **38**(10): p. 2640-5.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

42. Janjua, N., et al., *Late endovascular revascularization in acute ischemic stroke based on clinical-diffusion mismatch.* AJNR Am J Neuroradiol, 2009. **30**(5): p. 1024-7.
43. Natarajan, S.K., et al., *Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes.* Stroke, 2009. **40**(10): p. 3269-74.
44. Zaidi, S., et al. *Intra-arterial Treatment for Acute Anterior Circulation Ischemic Strokes Due to Large Vessel Occlusion Beyond 8 Hours – Preliminary Results.* in European Stroke Conference. 2008. Nice, France.
45. Rai, A.T., et al., *Endovascular therapy yields significantly superior outcomes for large vessel occlusions compared with intravenous thrombolysis: is it time to randomize?* Journal of NeuroInterventional Surgery, 2012.
46. Rai, A.T., et al., *Pre-intervention triage incorporating perfusion imaging improves outcomes in patients undergoing endovascular stroke therapy: a comparison with the device trials.* Journal of NeuroInterventional Surgery, 2013. **5**(2): p. 121-127.
47. Turk, A.S., et al., *Utilization of CT perfusion patient selection for mechanical thrombectomy irrespective of time: a comparison of functional outcomes and complications.* Journal of NeuroInterventional Surgery, 2012.
48. Rivero-Arias, O., et al., *Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome.* Medical decision making, 2010. **30**(3): p. 341-354.
49. Hong, K.-S. and J.L. Saver, *Quantifying the Value of Stroke Disability Outcomes WHO Global Burden of Disease Project Disability Weights for Each Level of the Modified Rankin Scale.* Stroke, 2009. **40**(12): p. 3828-3833.
50. Castano, C., et al., *Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation: a pilot study.* Stroke, 2010. **41**(8): p. 1836-40.
51. Roth, C., et al., *Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions.* Stroke, 2010. **41**(11): p. 2559-2567.
52. Mpotaris, A., et al., *Mechanical thrombectomy in severe acute stroke: preliminary results of the Solitaire stent.* Journal of Neurology, Neurosurgery & Psychiatry, 2012. **83**(1): p. 117-118.
53. Galimianis, A., et al., *Endovascular therapy of 623 patients with anterior circulation stroke.* Stroke, 2012. **43**(4): p. 1052-1057.
54. Flint, A.C., et al., *Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials.* Stroke, 2007. **38**(4): p. 1274-80.
55. Tarr, R., et al., *The POST Trial: Initial Post-Market Experience of the Penumbra System: Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke in the United States and Europe.* Journal of NeuroInterventional Surgery, 2010. **2**(): p. 341-344.
56. Dávalos, A., et al., *Retrospective multicenter study of Solitaire FR for revascularization in the treatment of acute ischemic stroke.* Stroke, 2012. **43**(10): p. 2699-2705.
57. Wahlgren, N., et al. *Final Results From The Trevo Study (Thrombectomy REvascularization of large Vessel Occlusions in acute ischemic stroke).* in International Stroke Conference. 2012. New Orleans, LA.
58. Broderick, J.P., et al., *Endovascular therapy after intravenous t-pa versus t-pa alone for stroke.* New England Journal of Medicine, 2013. **368**(10): p. 893-903.
59. Kidwell, C.S., et al., *A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke.* New England Journal of Medicine, 2013. **368**(10): p. 914-923.
60. Ciccone, A., et al., *Endovascular Treatment for Acute Ischemic Stroke.* New England Journal of Medicine, 2013. **368**(10): p. 904-913.
61. Albuquerque, F.C., et al., *The tribulations of stroke trials.* Journal of NeuroInterventional Surgery, 2013. **5**(3): p. 181-183.
62. SIR. *Society of Interventional Radiologists letter re: Use of Thrombectomy Devies for the Emergent Treatment of Acute Ischemic Stroke.* 2013; Available from: <http://www.sirweb.org/misc/SIRLetter%20CTAF%20STROKE%20Mar2013.pdf>.
63. Wisco, *Addition of MRI for Patient Selection in Intra-arterial Stroke Therapy Leads to Better Clinical Outcomes, a Pre-Post Study in International Stroke Conference Oral Abstracts; A161.* 2012.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

64. Kidwell, C.S., J.R. Alger, and J.L. Saver, *Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging*. Stroke, 2003. **34**(11): p. 2729-35.
65. Donnan, G.A., et al., *Penumbral selection of patients for trials of acute stroke therapy*. Lancet Neurol, 2009. **8**(3): p. 261-9.
66. Saver, J.L., *Time is brain--quantified*. Stroke, 2006. **37**(1): p. 263-6.
67. Leiva-Salinas, C., et al., *Tissue at risk in acute stroke patients treated beyond 8 h after symptom onset*. Neuroradiology, 2013: p. 1-6.
68. Abou-Chebl, A., *Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients*. Stroke, 2010. **41**(9): p. 1996-2000.
69. Wechsler, L.R., et al., *Factors influencing outcome and treatment effect in PROACT II*. Stroke, 2003. **34**(5): p. 1224-9.
70. Khatri, P., et al., *Good clinical outcome after ischemic stroke with successful revascularization is time-dependent*. Neurology, 2009. **73**(13): p. 1066-72.
71. Nogueira, R.G., et al., *Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials*. Stroke, 2009. **40**(12): p. 3777-83.
72. Nogueira, R.G., et al. *Endovascular Therapy for AIS Due to Proximal Arterial Occlusion Treated Beyond 8 Hours from Time Last Seen Well: A Subset Analysis of the Merci Registry*. in Eighth Society of NeuroInterventional Surgery (SNIS) Annual Meeting. 2011. Colorado Springs, Colorado, USA.
73. Jung, S., et al., *Safety of endovascular treatment beyond the 6-h time window in 205 patients*. European Journal of Neurology, 2013.
74. Nogueira, R.G., et al., *Neither Time to Treatment Nor the Use of Adjunctive Intra-arterial Thrombolytics Increase the Risk for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of CT Perfusion or MRI-selected Stroke Patients Treated at Late Time Windows: Analysis of the Pre-DAWN Dataset*. ISC:A93. 2010: Austin, Tx.
75. STAIR. *Stroke Treatment Academic Industry Roundtable*. March 9-10, 2013. Washington D.C. "Accelerating the Evolution of Stroke Therapy". In Press. 2013.
76. Wolpert, S.M., et al., *Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator*. The rt-PA Acute Stroke Study Group. AJNR Am J Neuroradiol, 1993. **14**(1): p. 3-13.
77. Shi, Z.-S., et al., *Endovascular Thrombectomy for Acute Ischemic Stroke in Failed Intravenous Tissue Plasminogen Activator Versus Non-Intravenous Tissue Plasminogen Activator Patients Revascularization and Outcomes Stratified by the Site of Arterial Occlusions*. Stroke, 2010. **41**(6): p. 1185-1192.
78. Davalos, A., et al., *The clinical-DWI mismatch: a new diagnostic approach to the brain tissue at risk of infarction*. Neurology, 2004. **62**(12): p. 2187-92.
79. Ebinger, M., et al., *Clinical-diffusion mismatch and benefit from thrombolysis 3 to 6 hours after acute stroke*. Stroke, 2009. **40**(7): p. 2572-4.
80. Lansberg, M.G., et al., *Evaluation of the clinical-diffusion and perfusion-diffusion mismatch models in DEFUSE*. Stroke, 2007. **38**(6): p. 1826-30.
81. Nogueira, R.G., et al., *Clinical-Diffusion Mismatch Better Discriminates Infarct Growth than MTT-DWI Mismatch in Patients with MCA-M1 Occlusion and Limited Infarct Core*. AJNR, 2013 (Submitted March).
82. Prosser, J., et al., *Clinical-diffusion mismatch predicts the putative penumbra with high specificity*. Stroke, 2005. **36**(8): p. 1700-4.
83. Albers, G.W., et al., *Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study*. Ann Neurol, 2006. **60**(5): p. 508-17.
84. Lansberg, M.G., et al., *Results of DEFUSE 2: Imaging Endpoints*. Stroke.2012;43:A52, 2012.
85. Mishra, N.K., et al., *Mismatch-based delayed thrombolysis: a meta-analysis*. Stroke, 2010. **41**(1): p. e25-33.
86. Dani, K.A., et al., *Systematic review of perfusion imaging with computed tomography and magnetic resonance in acute ischemic stroke: heterogeneity of acquisition and postprocessing parameters: a*

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- translational medicine research collaboration multicentre acute stroke imaging study.* Stroke, 2012. **43**(2): p. 563-6.
87. Goyal, M., B.K. Menon, and C.P. Derdeyn, *Perfusion Imaging in Acute Ischemic Stroke: Let Us Improve the Science before Changing Clinical Practice.* Radiology, 2013. **266**(1): p. 16-21.
88. Jovin, T.G., et al., *The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion.* Stroke, 2003. **34**(10): p. 2426-33.
89. Nogueira, R.G., et al., *Infarct Volume Thresholds for Prediction of Independent Functional Outcomes after Acute Ischemic Stroke.* Stroke 2012. **43**: p. A4030.
90. Lansberg, M.G., et al., *MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study.* The Lancet Neurology, 2012.
91. Zaidi, S.F., et al., *Final infarct volume is a stronger predictor of outcome than recanalization in patients with proximal middle cerebral artery occlusion treated with endovascular therapy.* Stroke, 2012. **43**(12): p. 3238-3244.
92. Furlan, *Personal Communication to Tudor Jovin re: ProAct II - Outcomes by Occlusion Location and NIHSS.* T. Jovin, Editor. 2013.
93. Fischer, U., et al., *NIHSS score and arteriographic findings in acute ischemic stroke.* Stroke, 2005. **36**(10): p. 2121-5.
94. Lewandowski, C.A., et al., *Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial.* Stroke, 1999. **30**(12): p. 2598-605.
95. DeGraba, T.J., et al., *Progression in acute stroke value of the initial NIH Stroke Scale score on patient stratification in future trials.* Stroke, 1999. **30**(6): p. 1208-1212.
96. Ringleb, P.A., et al., *Thrombolytic therapy for acute ischaemic stroke in octogenarians: selection by magnetic resonance imaging improves safety but does not improve outcome.* Journal of Neurology, Neurosurgery & Psychiatry, 2007. **78**(7): p. 690-693.
97. Mishra, N.K., et al., *Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA).* Stroke, 2010. **41**(12): p. 2840-8.
98. Bath, P.M., et al., *Statistical analysis of the primary outcome in acute stroke trials.* Stroke, 2012. **43**(4): p. 1171-1178.
99. Fisher, M., et al., *Stroke Therapy Academic Industry Roundtable IV. Enhancing the development and approval of acute stroke therapies: stroke therapy academic industry roundtable.* Stroke, 2005. **36**(8): p. 1808-1813.
100. Krams, M., K.R. Lees, and D.A. Berry, *The Past Is the Future Innovative Designs in Acute Stroke Therapy Trials.* Stroke, 2005. **36**(6): p. 1341-1347.
101. Shuaib, A., et al., *Partial Aortic Occlusion for Cerebral Perfusion Augmentation Safety and Efficacy of NeuroFlo in Acute Ischemic Stroke Trial.* Stroke, 2011. **42**(6): p. 1680-1690.
102. Kaufmann, e.a., *Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients.* Radiology, 2007. **243**: p. 812-819.
103. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.* N Engl J Med, 2008. **359**(13): p. 1317-29.
104. Chaisinanunkul , N., et al. *Adopting a Patient-Centered Approach to Primary Outcome Analysis of Acute Stroke Trials Using a Utility-Weighted Modified Rankin Scale.* Stroke. 2015. **46**:2238-2243

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 uninvolvled 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 uninvolvled 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.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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,

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

- 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 \geq 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 \geq 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 ($\geq 2/3$) 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 unininvolved other bed of the same vessel or the opposite cerebral artery

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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 $\geq 50\%$ 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 unininvolved other bed of the same vessel or the opposite cerebral artery.

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Appendix D. Informed Consent Form Template [attached]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Investigational Plan

Document Number: CDM10000146

Rev: AD

Appendix F. Adaptive Design Plan [attached]

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Summary of Changes to DAWN IDE Study Protocol

Study Name:	DAWN™ Trial
Study Number:	CDM10000146
Device:	Trevo® Retriever
Protocol Title:	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention
Protocol Version Number:	CDM10000146; 14 Sep 2015 Rev AB
Issue Date Protocol Revision:	28 April 2016 Rev: AC
Required Approvals:	FDA approval required: Yes Health Authorities notification required, if applicable: Yes Revision of the Case Report Form required: No Revision of the informed consent form required: No

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Throughout Protocol Page 1	<p>Version Information:</p> <p>Prevision revision: CDM10000146 Rev AB</p> <p>Date(s) of Amendment(s): 14 Sep 2015 Rev: AB</p>	<p>Version Information:</p> <p>Prevision revision: CDM10000146 Rev AC, including date of revision, throughout document</p> <p>Date(s) of Amendment(s): 14 Sep 2015 Rev: AB, 28 April 2016 Rev: AC</p> <p>The Table of Contents is also updated for the changes described herein.</p>	The changes described are from revision CDM10000146, Revision AB to Revision AC (the subject of this submission).
General Exclusion Criteria #6 Page 6 Page 35	Baseline hemoglobin counts of <7 mmol/L	Baseline hemoglobin counts of <7 mmol/L (11.28 g/dL)	Both mmol/L and g/dL are provided for clarification.
General Exclusion Criteria #10 Page 6 Page 35	Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal. Patients on factor Xa inhibitor for 24-48 hours ago must have a normal PTT .	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.	Modified PTT level criteria for patients on factor Xa to maintain consistency with prior statement in exclusion criteria #10.
Exclusion Criteria (additional information) Page 6	<ol style="list-style-type: none"> 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. 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. 	<ol style="list-style-type: none"> 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. 	Formatting correction made to distinguish #2 and #3 under “Exclusion Criteria (Additional information)”.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Concomitant Medication Therapies Page 7 7.7 Concomitant Medications and Management Page 45	<u>Treatment Arm:</u> 1. Use of IV or IA lytics, or IV or IA antiplatelets is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed.	<u>Treatment Arm:</u> 1. Use of IV or IA lytics, or IV or IA antiplatelets except aspirin is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed	A correction was made to Treatment Arm #1 under “Concomitant Medication Therapies” to clarify that although IV or IA lytics or IV or IA antiplatelets will be excluded to prevent confounding of treatment effect and to reduce the likelihood of hemorrhage post-procedure, use of aspirin is allowed.
Concomitant Medication Therapies # 1 Page 7 7.7 Concomitant Medications and Management Page 46	<u>Both Arms:</u> Aspirin 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.	<u>Both Arms:</u> 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.	Clarification on administration route for Aspirin.
7.2 Prior to Randomization Page 37	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): <ul style="list-style-type: none"> • Confirmation that all inclusion and none of the exclusion criteria have been met • Demographics and medical history • Neurological examination • Platelets/PT/PTT/INR/blood glucose • 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 contraindicated 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 	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): <ul style="list-style-type: none"> • 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 contraindicated 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 	Hemoglobin, sodium, and potassium concentration were added to the list of pre-procedure data required to maintain consistency with lab collection requirements at baseline.
8.6 Interim Analysis Page 53	Primary endpoint interim analyses will begin after 150 subjects have been enrolled and completed their study participation , and subsequent interim analyses will take place after every 50 subjects.	Primary endpoint interim analyses will begin after 150 subjects have been enrolled, and subsequent interim analyses will take place after every 50 subjects.	This correction was made to align with the Adaptive Design Plan (Appendix F to the protocol), which uses a statistical model designed for interim looks based upon subject enrollment.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
11.2 Adverse Events Reporting Requirements Page 60	All deaths shall be reported to the IRB no later than 24-48 hours of becoming aware	All deaths shall be reported to IRB/ EC no later than 24-48 hours of becoming aware or per the IRB/EC reporting requirements.	FDA requested the additional language that all deaths be reported to the IRB/EC no later than 24-48 hours of becoming aware. Most IRBs/ECs only required reporting of procedure- or device-related deaths. Therefore, additional clarification has been provided to be consistent with IRB/EC reporting requirements.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
11.4 Reporting to Regulatory Authorities / IRBs / ECs / Investigators Page 61	N/A	<p>For Canadian sites, Health Canada Mandatory Problem Reporting requirements as stated in the Medical Device Regulations must be followed:</p> <p>The manufacturer and importer of a medical device are required to report any event that is:</p> <ul style="list-style-type: none"> • 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 <p>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.</p> <p>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:</p> <ul style="list-style-type: none"> • SAEs occurring in Germany must be reported to BfArM <u>immediately</u> if a causal relationship between the SAE and the investigational medical device <u>cannot be excluded</u>. • An overall assessment of all SAEs must be reported to BfArM <u>quarterly</u>. <p>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.</p>	Per the request of Canada and Germany regulatory agencies (Health Canada and BfArM, respectively), reporting requirements have been added to the protocol.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Appendix B. Definitions Serious Adverse Event (SAE) Page 86	<ul style="list-style-type: none"> NOTE 2 – A planned hospitalization for a pre-existing condition or a condition required by the protocol, without serious deterioration in health is not considered serious. 	<ul style="list-style-type: none"> 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. 	Clarification to the definition of Serious Adverse Event (SAE) has been provided.

Summary of Changes to DAWN IDE Study Protocol

Study Name:	DAWN™ Trial
Study Number:	CDM10000146
Device:	Trevo® Retriever
Protocol Title:	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention
Protocol Version Number:	CDM10000146; 24 Apr 2014 Rev AA
Issue Date Protocol Revision:	14 Sep 2015 Rev: AB
Required Approvals:	FDA approval required: Yes Health Authorities notification required, if applicable: Yes Revision of the Case Report Form required: Yes Revision of the informed consent form required: No

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Throughout Protocol Page 1	Version Information: Revision revision: CDM10000146, Rev AA Page 1 – Study Information: Date/version: 24 Apr 2014 Rev: AA Date of Amendment(s): N/A	Version Information: Update header from CDM10000146, Rev AA to CDM10000146, Rev AB, including date of revision, throughout document. Page 1 – Study Information: Date of Amendment(s): 14 Sep 2015 Rev: AB The Table of Contents is also updated for the changes described herein.	The changes described are from revision CDM10000146, Revision AA to Revision AB (the subject of this submission).
Study Responsibility Page 1	Cindy Jahans Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: cindy.jahans@stryker.com Tel: (510) 413-2268 e-Fax: (855) 328-1403	Christine Yang Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: christine.yang@stryker.com Tel: (510) 413-2841 e-Fax: (855) 328-1403	A new project manager has been assigned to the study by Stryker NV.
Protocol Synopsis Device Sizes Page 3	<i>4 mm x 20 mm and 3 mm x 20 mm (additional sizes may be included in the study as they become available)</i>	N/A (Row removed from tabular summary)	The Description of Device Sizes was removed from the Protocol Synopsis to streamline this section; the necessary detail is provided in Section 2.1, Study Device Description.
Protocol Synopsis Follow-up Schedule Page 5	<i>All follow up time points are relative to time of randomization (time zero):</i>	<i>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.</i>	Additional verbiage was added to clarify the timeframe that is considered to be “baseline” for the purposes of recording study data (e.g., lab values) in the event that hospital transfer occurs prior to randomization.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Identical original text appears in two locations: <ul style="list-style-type: none"> • Protocol Synopsis General Inclusion Criteria Page 5 • Section 6.1 Inclusion Criteria Page 33 	<p>3. Baseline NIHSS ≥ 10 (assessed within one hour prior to measuring core infarct volume)</p>	<p>3. Baseline NIHSS ≥ 10 (assessed within one hour of measuring core infarct volume)</p>	<p>Verbiage was corrected to align with intended instructions and to be consistent with language throughout the protocol.</p>
Identical original text appears in two locations: <ul style="list-style-type: none"> • Protocol Synopsis General Inclusion Criteria Page 5 • Section 6.1 Inclusion Criteria Page 33 	<p>8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form*</p> <p>* If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if representative or person of trust is available. 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.)</p>	<p>8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form*</p> <p>* 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.)</p>	<p>The footnote to General Inclusion Criterion #8 was moved to a more visually prominent location and the wording was modified to allow the use of emergency informed consent procedures in accordance with recent changes in French laws.</p>
Identical original text appears in two locations: <ul style="list-style-type: none"> • Protocol Synopsis Imaging Inclusion Criteria Page 5 • Section 5.2.5 Justification for Use of Clinical Imaging Mismatch Criteria Page 30 • Section 6.1 Imaging Inclusion Criteria Page 33 	<p>3. Clinical Imaging Mismatch (CIM) defined as one of the following on RAPID MR-DWI or CTP-rCBF maps:</p> <ol style="list-style-type: none"> 0-20 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old) 0-30 cc core infarct and NIHSS ≥ 10 (and age < 80 years old) 31 cc to ≤ 50 cc core infarct and NIHSS ≥ 20 (and age < 80 years old) 	<p>3. Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps:</p> <ol style="list-style-type: none"> 0-21 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old) 0-31 cc core infarct and NIHSS ≥ 10 (and age < 80 years old) 31 cc to ≤ 51 cc core infarct and NIHSS ≥ 20 (and age < 80 years old) 	<p>The upper limit of CIM categories (a) and (b) was increased by one whole number to clarify for participating clinical sites that decimal values between 20.0 and 20.9 fall into category (a) while decimal values between 30.0 and 30.9 fall into category (b).</p> <p>The term "RAPID" was deleted as a reference to a specific type of core infarct imaging software (see item #13 below for justification).</p>
Identical original text appears in two locations: <ul style="list-style-type: none"> • Protocol Synopsis General Exclusion Criteria Page 6 • Section 6.2 General Exclusion Criteria Page 34 	<p>7. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal; If factor Xa inhibitor (e.g. apixaban) < 24 hrs ago must have normal ecarin clotting time and if 24-48 hrs ago must have normal PTT.</p>	<p>10. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal. If factor Xa inhibitor 24-48 hours ago must have a normal PTT.</p>	<p>General exclusion criterion #7 was modified to remove reference to ecarin clotting time (ECT), as its measurement is no longer a standard of care in stroke onset management.</p>

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Identical original text appears in two locations: <ul style="list-style-type: none"> Protocol Synopsis General Exclusion Criteria Page 6 Section 6.2 General Exclusion Criteria Page 34 	N/A	<p>6. Baseline hemoglobin counts of <7 mmol/L</p> <p>8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L</p>	Per FDA request, hemoglobin counts, electrolyte parameters (sodium concentrations, and potassium concentrations) have been added as general exclusion criteria in order to exclude patients who may have increased risks of mortality and morbidity if randomized for treatment with the study device.
Identical original text appears in two locations: <ul style="list-style-type: none"> Protocol Synopsis General Exclusion Criteria Page 6 Section 6.2 General Exclusion Criteria Page 34 	13. Current participation in another investigational drug or device study or registry	13. Current participation in another investigational drug or device study	General exclusion criterion #13 was modified to allow for study participation in registry.
Identical original text appears in two locations: <ul style="list-style-type: none"> Protocol Synopsis Imaging Exclusion Criteria Page 6 Section 6.2 Imaging Exclusion Criteria Page 34 	2. Evidence of internal carotid artery flow limiting dissection on CTA/MRA	<p>N/A</p> <p>(Criterion removed from Imaging Exclusion Criteria)</p> <p>(All subsequent Imaging Exclusion Criteria have been renumbered due to removal of original Imaging Exclusion Criterion #2.)</p>	Imaging Exclusion Criterion #2 has been incorporated into modified Exclusion Criterion #3 (see justification below.)
Identical original text appears in two locations: <ul style="list-style-type: none"> Protocol Synopsis Imaging Exclusion Criteria Page 6 Section 6.2 Imaging Exclusion Criteria Page 34 	3. Severe proximal extra-cranial carotid artery stenosis, or occlusion of any etiology, where concurrent vessel angioplasty or stenting is expected to be necessary and the procedure cannot be delayed until after the 24 (-6/+24) hour assessments have been completed	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).	Imaging Exclusion Criterion #3 was modified to reflect current best practices as implemented in other global stroke trials (e.g., SWIFT PRIME ¹).

¹ Saver JL, Goyal M, Bonafe A, et al.; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *NEJM*. 2015 Jun 11;372(24):2285-95. Epub 2015 Apr 17.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Identical original text appears in two locations: <ul style="list-style-type: none"> Protocol Synopsis Imaging Exclusion Criteria Page 6 Section 6.2 Imaging Exclusion Criteria Page 34 	<p>8. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) as confirmed on CTA/MRA, or clinical evidence of bilateral strokes or strokes in multiple territories</p>	<p>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</p>	<p>Imaging Exclusion Criterion #8 was modified to clarify vertebrobasilar system.</p>
Identical original text appears in two locations: <ul style="list-style-type: none"> Protocol Synopsis Concomitant Medication Therapies Page 7 Section 7.7 Concomitant Medications and Management Pages 47 	<p><u>Treatment Arm</u></p> <p>1. Use of IV or IA lytics, or antiplatelets is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed.</p> <p><u>Both Arms</u></p> <p>6. Newly administered aspirin is the only anti-platelet 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.</p> <p>7. Subjects previously treated with antiplatelet agents or combination antiplatelet therapy (e.g. for a previously implanted drug eluting stent), may continue this regimen after post procedure imaging is completed if in the investigator's opinion the benefits of continued therapy outweigh the risks of potential neurological deterioration related to hemorrhage.</p>	<p><u>Treatment Arm, Item #1:</u></p> <p>1. Use of IV or IA lytics, or IV or IA antiplatelets is prohibited in subjects randomized to the treatment arm during the procedure and until after follow up imaging is completed.</p> <p><u>Both Arms, Item #6:</u></p> <p>6. Aspirin 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.</p> <p>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.</p>	<p>The Treatment Arm (Item #1) verbiage was modified to clarify that intravenous (IV) or intraarterial (IA) administration of antiplatelets, as well as lytics, are prohibited until follow-up imaging is completed.</p> <p>Both Arms (Item #6 and 7) verbiage was modified to allow Clopidogrel administration for anti-platelet treatment, in accordance with published AHA/ASA recommendations.²</p> <p>Clarification of antiplatelet therapy regimen was modified.</p>
Section 2.1 Study Device Description Page 15	<p>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.</p>	<p>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. 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.</p>	<p>Table 1 was added to the Study Device Description section to provide additional clarity regarding key dimensions of currently available study devices. New verbiage was added to clarify that additional sizes may become available following regulatory approvals, but that only devices labeled for investigational use are to be used by participating clinical trial sites.</p>
Section 2.1 Study Device Description Page 16	<p>Figure 1. Trevo Retrievers under fluoroscopy</p>	<p>Figure 1. Examples of Trevo Retrievers</p>	<p>Figure 1 was modified to the Study Device Description section to provide additional clarity regarding currently available study devices.</p>

² Furie KL, Kasner SE, Adams RJ, et al.; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011 Jan;42(1):227-76. Epub 2010 Oct 21.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 2.2 Study Device Labeling Page 17	<p><i>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, and is attached as Appendix E.</i></p>	<p><i>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.</i></p>	The wording change clarifies that the IFU appended to study protocol rev AB is a sample, and that current IFUs will be packaged with each study device.
Section 5.1 Overview Pages 19-20	<p>Figure 3 shows the flow of subjects through the screening, randomization assignment and follow up phases of the study.</p> <p>Clinical Imaging:</p> <ul style="list-style-type: none"> a. 0-20 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old) b. 0-30 cc core infarct and NIHSS ≥ 10 (and age < 80 years old) c. >30 cc to ≤ 50 cc core infarct and NIHSS ≥ 20 (and age < 80 years old) <p>Control Arm – Medical Management Only: Manage patient per institution's usual standard of care for AIS patients presenting beyond 6 hrs from TSLW</p> <p>Both Arms: NIHSS to assess for SICH (NIHSS within 24hr)</p>	<p>Figure 2 shows the flow of subjects through the screening, randomization assignment and follow up phases of the study.</p> <p>Clinical Imaging:</p> <ul style="list-style-type: none"> 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 < 80 years old) <p>Control Arm – Medical Management Only: Manage patient per protocol for AIS patients presenting beyond 6 hrs from TSLW</p> <p>Both Arms: NIHSS to assess for SICH (attempt to complete within 2hrs of imaging)</p>	The change in cross-reference from Figure 3 to Figure 2 corrects a typographical error. Clinical Imaging criteria were updated in Figure 2 to align with change made to Imaging Inclusion Criterion #3 (as previously described in item 6). The medical management protocol for control arm patients was updated to specify that patients were to be managed per protocol in order to standardize practices across all participating U.S. and international clinical sites. Clarification of SICH assessment and timing of NIHSS.
Section 5.2.1 Justification for Expansion of Time Window Pages 22-25	<p>The results of this comparison are summarized in Table .</p> <p>Table 2. Merci Registry</p> <p>The results of this comparison are summarized on Table below.</p> <p>Table 3. Pre-DAWN Cohort vs. PROACT II Treatment and Control Arm</p>	<p>The results of this comparison are summarized in Table .</p> <p>Table 3. Merci Registry</p> <p>The results of this comparison are summarized on Table below.</p> <p>Table 4. Pre-DAWN Cohort vs. PROACT II Treatment and Control Arm</p>	Update numbering sequence of Table and Table reference.
Section 5.2.5 Justification for Use of Clinical Imaging Mismatch Criteria Page 30	<p>a. 0-20 cc core infarct and NIHSS ≥ 10 (and ≥ 80 years old)</p> <p>b. 0-30 cc core infarct and NIHSS ≥ 10 (and < 80 years old)</p> <p>c. 31 cc to ≤ 51 cc core infarct and NIHSS ≥ 20 (and < 80 years old)</p>	<p>a. 0-<21 cc core infarct and NIHSS ≥ 10 (and ≥ 80 years old)</p> <p>b. 0-<31 cc core infarct and NIHSS ≥ 10 (and < 80 years old)</p> <p>c. 31 cc to <51 cc core infarct and NIHSS ≥ 20 (and < 80 years old)</p>	Revision to Clinical Imaging Mismatch (CIM) subgroups as defined earlier in the protocol synopsis and various sections of the protocol.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
<p>Section 5.2.6 Justification for Use of RAPID Imaging Software Page 30</p>	<p>5.2.6 Justification for Use of Standardized RAPID Imaging Software <i>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 RAPID software (iSchemaView, Palo Alto, CA) which will be installed at each site, and on all CT/MR scanners used to screen subjects. Note: RAPID software is to be used for research purposes only, and is not to be used for routine clinical assessment of images for patients who are not being screened for the DAWN study.</i></p> <p>RAPID 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.</p> <p>The CT/MR Core Lab will verify, and record, the core infarct volumes generated by RAPID 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.</p> <p>The RAPID software has been 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. 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 RAPID processed images used to qualify the subject for the study.</p>	<p>5.2.6 Justification for Use of Standardized Core Infarct Imaging Software <i>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).</i></p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>Section 5.2.6 has been updated to allow for use of an alternative FDA-cleared software platform (Olea Sphere) at participating clinical trial sites, consistent with clinical trial practices implemented in several other global stroke trials.</p> <p>Accordingly, the term "RAPID" (when used in conjunction with a reference to the core infarct imaging software) has been removed from the protocol.</p>

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 5.2.7 Justification for Use of Weighted mRS as Primary Endpoint Page 31	N/A	104. Chaisinanunkul , N., et al. Adopting a Patient-Centered Approach to Primary Outcome Analysis of Acute Stroke Trials Using a Utility-Weighted Modified Rankin Scale. <i>Stroke.</i> 2015; 46:2238-2243	Added reference to recent publication supporting use of weighted mRS.
Section 5.4 Blinding and Breaking the Blind Page 32	<i>Core infarct volume at baseline will be measured by automated calculations, using standardized software (RAPID) at each participating site.</i>	<i>Core infarct volume at baseline will be measured by automated calculations, using standardized software at each participating site.</i>	The term “RAPID” (when used in conjunction with a reference to the core infarct imaging software) has been deleted.
Section 7 Study Procedures Page 35	<i>The Time and Events schedule is outlined in Table 4.</i>	<i>The Time and Events schedule is outlined in Table 5.</i>	Update numbering sequence of Table and Table reference.
Section 7.1 Written Informed Consent Pages 35-36	<p><i>Note - If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if, representative or person of trust is available. 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.)</i></p> <p><i>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, either before the routine, standard of care baseline imaging is performed to assess the subject for hemorrhage and large vessel occlusion status, or after the baseline imaging is performed but before the baseline images are sent to the RAPID software to measure the core infarct volume. The Informed Consent Form (ICF) must be approved by the study Institutional Review Board (IRB)/Ethics Committee (EC). 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.</i></p> <p><i>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 will be entered into the electronic database and their reason(s) for screen failure will be documented, but they will not be followed beyond the screening visit, and no further data will be collected/recorded.</i></p>	<p><i>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.)</i></p> <p><i>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. 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.</i></p> <p><i>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.</i></p>	<p>The wording regarding informed consent was modified to allow the use of emergency informed consent procedures in accordance with recent changes in French laws.</p> <p>Clarified that although screen failed subjects will be documented, that due to technical efficiencies, that the screen failures may not be tracked in the same eCRF database as enrolled subjects. This allows for manual or other logging mechanisms for screen failed subjects.</p>

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 7.1 Written Informed Consent Page 36	N/A (Citation previously not entered)	<i>1 Food and Drug Administration. Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers. Guidance for Industry. Draft Guidance issued March, 2015.</i>	Footnote has been inserted to provide reference to the FDA Guidance that was released in March 2015 regarding use of Electronic Informed Consent.
Section 7.2 Prior to Randomization Page 36	<p><i>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.</i></p> <p><i>Refer to Table , DAWN Study Time and Events Schedule, Table 4. DAWN™ Trial Time and Events Schedule</i></p> <p>*NIHSS should be obtained within 1 hour of corresponding core infarct measurement.</p> <p>** NIHSS should be obtained within 2 hours of the 24 (-6/+24) hour neuro-imaging to determine presence/absence of hemorrhage.</p> <p>† mRS must be conducted by an individual blinded to the treatment arm.</p> <p>*** CT/MR and Angiographic images should be de-identified before being submitted to Stryker NV or core lab.</p>	<p><i>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.</i></p> <p><i>Refer to Table , DAWN Study Time and Events Schedule Table 5. DAWN™ Trial Time and Events Schedule</i></p> <p>*NIHSS within 1 hour of corresponding core infarct measurement.</p> <p>** NIHSS should be obtained within approximately 2 hours of the 24 (-6/+24) hour neuro-imaging to determine presence/absence of hemorrhage.</p> <p>† mRS must be conducted by an individual blinded to the treatment arm.</p> <p>†† Randomization should occur within 1 hour of obtaining neuro imaging used to determine core infarct measurement.</p> <p>*** CT/MR and Angiographic images should be de-identified before being submitted to Stryker NV or core lab.</p>	<p>The definition of the baseline period was added for further clarification and to ensure consistency across clinical trial sites.</p> <p>Update numbering sequence of Table and Table reference.</p> <p>Revision of Footnotes in Table 5 to correspond with Protocol Synopsis and Section 5.1</p>
Section 7.3.1 Diagnostic Angiography Page 39	<p><i>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.</i></p>	<p><i>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.</i></p>	New verbiage was added to clarify that injection is not required if it poses unacceptable risk or delays.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
<p><i>Section 7.3.2</i> <i>Unexpected Diagnostic Angiography Findings</i> <i>Page 41</i></p>	<p><i>B. If thrombus is identified in one or more proximal non treatable arteries per protocol and 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:</i></p> <p><i>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.</i></p> <p><i>2. 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.</i></p>	<p><i>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:</i></p> <p>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.</p> <p>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.</p>	<p>Insert “in” to further define condition of unexpected diagnostic angiography finding.</p> <p>Due to known inter assessor variability and overlapping definitions of M1 vs M2 location as assessed via angiography (as noted in several recent randomized AIS studies), clarified that core lab determination of M2 conflicting with investigator diagnosis of M1 will not be a protocol violation. Stryker will report both site assessed and core lab assessed clot location. Final determination will be based on core lab assessment only.</p>

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 7.4 Trevo Thrombectomy Procedure (Treatment arm only) Page 44	<p>a. If reperfusion has been successful with the Trevo Retriever (defined as at least modified TICI 2b in the territory treated)</p> <p>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.</p>	<p>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)</p> <p>If adjunctive treatment (rescue therapy) is used AFTER the Trevo Retriever a biplane angiography should be performed immediately afterwards in order to reassess vessel patency and determine the effect of the adjunctive rescue treatment. Adjunctive therapy (e.g. use of another stent retriever or stent) is strongly discouraged and represents a major protocol deviation. Participants who receive rescue adjunctive therapy will be imputed as mRS = 6.</p>	<p>Removed requirement to terminate the procedure upon achieving modified TICI 2b in order to reflect current standard of care for reperfusion targets of at least TICI 2b and reperfusion of >2/3 MCA territory.</p> <p>Verbiage was added to clarify that adjunctive therapy is strongly discouraged and represents a major protocol violation.</p>
Section 7.5 End of the Trevo Thrombectomy Procedure (Treatment arm only) Page 44	3. Modified TICI grade 2b or 3flow is established	3. TICI grade 2b or 3flow (reperfusion of > 2/3 MCA territory) is established	Deletion of “Modified” and addition for definition of reperfusion.
Section 8.1 Sample Size Estimates and Justification Page 50	<p>The distribution of the mRS outcomes for the control arm used in the simulations is shown in 5.</p> <p>Table 5. Distribution of mRS outcomes for the control arm in the simulations</p>	<p>The distribution of the mRS outcomes for the control arm used in the simulations is shown in</p> <p>Table .</p> <p>Table 6. Distribution of mRS outcomes for the control arm in the simulations</p>	Update numbering sequence of Table and Table reference.
Section 8.4 Population Definitions Page 51	<i>Enrolled:</i> Includes any subject who has been randomized based upon the results of the RAPID 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).	<i>Enrolled:</i> 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)	Deletion of “RAPID” in the definition of the enrolled population.
Section 8.6 Interim Analysis Pages 52	Primary endpoint interim analyses will begin after 150 subjects have been enrolled, and subsequent interim analyses will take place after every 50 subjects.	Primary endpoint interim analyses will begin after 150 subjects have been enrolled and completed their study participation, and subsequent interim analyses will take place after every 50 subjects.	New verbiage was added to clarify that the first 150 subjects must have completed their study participation prior to initiation of interim data analyses.
Section 8.6.2 Enrichment Pages 53	The five possible subpopulations are defined by infarct size as measured using RAPID MR-DWI or CTP-rCBF maps:	The five possible subpopulations are defined by infarct size as measured using MR-DWI or CTP-rCBF maps:	Deletion of “RAPID” in the type of MRI and CT maps.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 11.1 Adverse Event Definitions and Classification Page 57-58	<p><i>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:</i></p> <p><i>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.</i></p> <p><i>Related - There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely.</i></p> <p><i>Unknown – There is not enough information to make a determination.</i></p> <p><i>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:</i></p> <p><i>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.</i></p> <p><i>Related - There is a strong relationship to index procedure, or recurs on re-challenge, and another etiology is unlikely.</i></p> <p><i>Unknown – There is not enough information to make a determination.</i></p>	<p><i>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:</i></p> <p><i>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.</i></p> <p><i>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.</i></p> <p><i>Probable - There is a strong relationship to the investigational product, or recurs on re-challenge, and another etiology is unlikely.</i></p> <p><i>Highly Probable - There is no other reasonable medical explanation for the event.</i></p> <p><i>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:</i></p> <p><i>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.</i></p> <p><i>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.</i></p> <p><i>Probable - There is a strong relationship to the index procedure, or recurs on re-challenge, and another etiology is unlikely.</i></p> <p><i>Highly Probable - There is no other reasonable medical explanation for the event.</i></p>	Revised adverse event categorization and definitions based on recommendation from FDA.
Section 11.2 Adverse Events Reporting Requirements Page 60	<p><i>All SAEs and UADEs shall be reported within 24 hours of becoming aware to Stryker Neurovascular via data entry into the CRFs. 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.</i></p>	<p><i>All SAEs and UADEs shall be reported within 24 hours of becoming aware to Stryker Neurovascular via data entry into the CRFs. All deaths shall be reported to the IRB no later than 24-48 hours of becoming aware. 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.</i></p>	New verbiage was added to clarify that all deaths shall be reported to the IRB no later than 24-48 hours of becoming aware.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 11.4 Reporting to Regulatory Authorities / IRBs / ECs / Investigators Page 61	N/A	<i>Stryker NV will identify sites at which adverse events (AEs) and protocol deviations occur in annual reports and correspondence with the FDA.</i>	Language added to clarify that Stryker NV will report particular sites at which AEs and protocol deviations occur in annual reports and/or correspondence to FDA.
Section 12.2.2 Trevo Thrombectomy Page 62	<i>Refer to the Instructions for Use (IFU) in Appendix E for table of previously observed rates of procedural risks.</i>	<i>Refer to the sample Instructions for Use (IFU) in Appendix E for table of previously observed rates of procedural risks.</i>	The word “sample” was added to clarify that the IFU is provided in Appendix E to the protocol as a sample only. IFUs applicable to the product received at each site will be provided in device packaging.
Section 13.1 Steering Committee: Page 63	<i>At the time of database lock the Steering Committee may select additional investigators, based on enrollment and adherence to the protocol, to participate on a Publication Committee.</i>	<i>The Steering Committee may select additional investigators, based on enrollment and adherence to the protocol, to participate on a Publication Committee.</i>	The Steering Committee may select additional investigators to participate in the Publication Committee prior to database lock; as such, the time specification “at the time of database lock” was removed from the protocol.
Section 13.2.2 Data Monitoring Committee (DMC) Page 64	<i>The DMC's role is to monitor and advocate for subject safety throughout the lifecycle of the trial and they will review all SAEs 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. 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 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.</i>	<i>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 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.</i>	Per FDA request, the DAWN study stopping rules have been updated to ensure the safety of the study and its participants.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Section 13.3 Imaging Core Labs Page 66	<p>Two central imaging core labs will be established to independently review CT/MR and angiographic images. One lab will review angiographic images from the procedure to determine revascularization and clot location.</p> <p>Another independent 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. Having a CT/MR core lab independent from the angiographic core lab ensures that the CT/MR core lab is blinded to the treatment.</p>	<p>The independent angiographic core lab will review angiographic images from the procedure to determine revascularization and clot location.</p> <p>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.</p>	The requirement for two separate central imaging core labs for angiographs and CT/MR images has been removed to improve process and cost efficiencies in handling images.
Section 13.3.1 Angiographic Core Lab Page 67	<p>For each enrolled subject, angiograms must be appropriately de-identified, and sent to Stryker NV for tracking, archiving and forwarding to the imaging core lab for evaluation.</p>	<p>For each enrolled subject, angiograms must be appropriately de-identified, and sent to the imaging core lab for evaluation.</p>	The requirement to forward angiograms to Stryker NV for processing has been removed to improve process and cost efficiencies in handling images. All images can be de-identified at the clinical trial sites and transmitted to the core lab directly by each site.
Section 13.3.2 CT/MR Core Lab Pages 67-68	<p>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 Error! Reference source not found..</p>	<p>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.</p>	Update numbering sequence of Table and Table reference.
Section 14.3 Written Informed Consent Form Pages 69	<p>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.</p> <p>Note - If approved by local ethics committee and country regulations, the investigator is allowed to enroll a patient if, representative or person of trust is available. 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.)</p>	<p>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.</p> <p>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.)</p>	The wording regarding informed consent was modified to include a reference to the updated FDA Guidance on the use of electronic informed consent.

Section of Protocol Modified	Existing Text as Written in DAWN Protocol: (CDM10000146, 24 Apr 2014, Rev AA)	Revised/New Text as Written in DAWN Protocol (CDM10000146, 14 Sep 2015, Rev AB)	Justification for Modification
Appendix B. Definitions Page 81-85	N/A (Definitions previously not entered)	<p><i>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.</i></p> <p><i>Intraprocedure Mortality: Death occurring during the index thrombectomy procedure</i></p> <p><i>In vivo (breakage) device failure: Breakage of the Trevo device in the vasculature during the index procedure.</i></p> <p><i>Neurological worsening: A 4 or more point increase in NIHSS from baseline. Neurological worsening could be new or evolution/progression of the index stroke.</i></p> <p><i>Stroke: An acute neurological event with focal symptoms and signs lasting ≥ 24 hours. Stroke can be sub-classified as Hemorrhagic or Ischemic.</i></p> <ul style="list-style-type: none"> • <i>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).</i> • <i>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.</i> <p><i>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.</i></p>	Appendix B has been updated to include a comprehensive list of definitions to be consistent with those found in the CEC Charter. Definitions of the following terms were added: intramural arterial dissection, intraprocedure mortality, in vivo (breakage) device failure, neurological worsening, stroke, hemorrhagic stroke, ischemic stroke, and vessel perforation.
Appendix E. Page 89	Appendix E. Proposed Instructions for Use (IFU) [attached]	Appendix E. Sample Instructions for Use (IFU) [attached]	Revised Header for Appendix to include current IFU.

Summary of Changes to DAWN IDE Study Protocol

Study Name:	DAWN™ Trial
Study Number:	CDM10000146
Device:	Trevo® Retriever
Protocol Title:	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention
Protocol Version Number:	CDM10000146; 14 Sep 2015 Rev AB; 28 April 2016 Rev: AC
Issue Date Protocol Revision:	26 Jan 2017 Rev: AD
Required Approvals:	FDA approval required: Yes Health Authorities notification required, if applicable: Yes Revision of the Case Report Form required: No Revision of the informed consent form required: No

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Study Responsibility Page 1	Christine Yang Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: christine.yang@stryker.com Tel: (510) 413-2841 e-Fax: (855) 328-1403	Christine Yang Toruno Clinical Project Manager Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538-6515 Email: christine. toruno @stryker.com Tel: (510) 413-2841 e-Fax: (855) 328-1403	Study Responsibility contact information updated.
Throughout Protocol, Page 1	Previous version: CDM10000146 Rev AC Date(s) of Amendment(s): 14 Sep 2015 Rev: AB, 28 April 2016 Rev: AC	Update header from CDM10000146, Rev AC to CDM10000146, Rev AD, including date of revision, throughout document Date(s) of Amendment(s): 14 Sep 2015 Rev: AB, 28 April 2016 Rev: AC, 26 Jan 2017 Rev: AD The Table of Contents is also updated for the changes described herein.	The changes described are from revision CDM10000146, Revision AC to Revision AD (the subject of this submission).
Protocol Synopsis Primary Endpoint Page 3	Difference between the average weighted modified Rankin scale score at 90 days between the active and control groups.	90-day disability assessed by the modified Rankin scale (mRS)	Clarified primary endpoint in order to distinguish from primary endpoint analysis.

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Protocol Synopsis Efficacy Parameter Page 4	Note: For purposes of primary efficacy analysis each mRS category will be assigned a numerical value representing its clinical utility, as follows:	Note: For purposes of primary efficacy weighted mRS analysis each mRS category will be assigned a numerical value representing its clinical utility, as follows:	This language was modified to distinguish that the weighted numerical value assigned to each mRS category will be used for the purposes of the weighted mRS analysis.
Protocol Synopsis Primary Statistical Null Hypothesis Page 7	The null hypothesis is that there is no difference in the average of the weighted mRS categories at 90 days in the Trevo Thrombectomy plus Medical Management group compared to Medical Management alone.	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.	To be consistent with the final analysis to be provided to FDA upon study conclusion, the null hypothesis was updated to include dichotomous analysis in addition to weighted mRS analysis.
Protocol Synopsis Statistical Test Method Page 7	The alternative hypothesis is that 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 weighted 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.	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.	To be consistent with the final analysis to be provided to FDA upon study conclusion, the alternative hypothesis was updated to include dichotomous analysis in addition to weighted mRS analysis.

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Section 2.1 Study Device Description Page 15	<p>Table 1. Key Dimensions of Trevo Family Retrievers</p> <p>Investigational Model # Column</p> <p>90191</p> <p>90192</p> <p>90193</p> <p>90194</p> <p>90195</p>	<p>Table 1. Key Dimensions of Trevo Family Retrievers</p> <p>Investigational Model # Column</p> <p>90191, 90291</p> <p>90192, 90292</p> <p>90193, 90293</p> <p>90194, 90294</p> <p>90195, 90295</p>	<p>The list of investigational model numbers in Table 1. Key Dimensions of Trevo Family Retrievers was updated to reflect all current model numbers available within the trial. Release of these additional model numbers was previously described in Attachment 2 of the Annual Progress Report dated March 16, 2016.</p>
Section 4.1 Primary Endpoint Page 18	<p>The primary endpoint is a comparison of the difference between the average weighted modified Rankin Scale (mRS) score at 90 days post randomization between the active and control groups. 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]</p>	<p>The primary endpoint is the 90-day disability 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]</p>	<p>To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was modified to include dichotomous analysis in addition to weighted mRS analysis as well as to distinguish the primary endpoint from the primary endpoint analysis.</p>

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Section 5.2.7 Justification for Use of Weighted mRS as Primary Endpoint Analysis Page 31	<p>5.2.7 Justification for Use of Weighted mRS as Primary Endpoint</p> <p>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]</p>	<p>5.2.7 Justification for Use of Weighted mRS as Primary Endpoint Analysis</p> <p>The primary endpoint is 90-day disability assessed by the modified Rankin Score (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).</p> <p>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]</p>	To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was added to distinguish the primary endpoint from the primary endpoint analysis as well as to clarify that both dichotomous analysis and weighted mRS analysis will be included.
Section 8.6.3 Interim Monitoring for Expected Success Page 54	<p>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 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.</p>	<p>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.</p>	To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was added to clarify that both dichotomous analysis and weighted mRS analysis will be included as primary analysis.

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Section 8.7 Statistical Analysis Page 54	The final analysis 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 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.	To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was added to clarify that both dichotomous analysis and weighted mRS analysis will be included.
Section 13.2.2 Data Monitoring Committee (DMC) Page 66	The DMC assessment of benefit versus harm will take into account 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 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.	To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was modified to include dichotomous analysis in addition to weighted mRS analysis.
Appendix F Page 1	An Enrichment Design for Stryker's Trevo Device, January 20, 2014	An Enrichment Design for Stryker's Trevo Device, January 26, 2017	Version Date has been updated.
Appendix F Section 1.0 Page 1	<i>[No text in previous version]</i>	The mRS score can also be dichotomized, where a score of 0 to 2 is counted as a success and a score of 3 to 6 is counted as a failure. This analysis method does a poorer job of measuring benefit to patients, but it has been popular historically. Dichotomized mRS also plays a role in the design by contributing to the sample size decisions. Specifically, the trial cannot stop early for expected success unless there is a high probability that the final data will demonstrate an mRS benefit to patients as measured both by the utility measure and by the dichotomous measure.	Updated expected success criteria to include success of dichotomous 90 day mRS analysis in addition to weighted mRS analysis. To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was modified to include dichotomous analysis in addition to weighted mRS analysis.
Appendix F Section 2.0 Trial Overview Page 2	Then we describe the Bayesian adaptive trial design including decision rules for patient enrichment and early stopping offering example trials to illustrate how it may proceed.	Then we describe the Bayesian adaptive trial design, including decision rules for patient enrichment and early stopping, while offering example trials to illustrate how it may proceed.	Grammar correction.

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Appendix F Section 3.3 Primary Endpoint Page 4	<i>[No text in previous version]</i>	Another possible method of analyzing the 90 day mRS endpoint involves using a dichotomized version of the utility function (weight of 10 for mRS of two or better, weight of zero for mRS of three or worse). We use this analysis method in early stopping decisions as described in section 4.3 and as an additional analysis method of the primary endpoint for the marketing application.	Updated expected success criteria to include success of dichotomous 90 day mRS analysis in addition to weighted mRS analysis. To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was modified to include dichotomous analysis in addition to weighted mRS analysis.
Appendix F Section 3.4 Primary Analysis Page 4	This is a flexible spline-like model that will capture that the average weighted mRS score in the control group is a (possibly non-linear) function of infarct size.	This is a flexible spline-like model that will capture that the average weighted mRS score in the control group as a (possibly non-linear) function of infarct size.	Grammar correction.
Appendix F 4.0 Prospectively Planned Interim Analyses Page 5	Five possible decisions may be made at interim analyses: 1. The trial may stop for either futility starting at the 150-patient analysis.	Five possible decisions may be made at interim analyses: 1. The trial may stop for futility starting at the 150-patient analysis.	Grammar correction.
Appendix F Section 4.2 Enrichment Page 6	Enrichment decisions are also based on the π_e 's defined above. The design will enrich if one of two conditions is met. First we calculate the effect size in the highest 5 included infarct sizes. If the current maximum allowable infarct size is $e=35$ or more, calculate the posterior probability the average treatment effect is positive for infarct sizes between $e-4$ and e . If the probability is less than 40%, enrich by only including patients with infarct sizes $e-5$ or less.	<i>[First sentence removed]</i> The design will enrich if one of two conditions is met. First we calculate the effect size in the highest 5 included infarct sizes. If the current maximum allowable infarct size is $e=35$ or more, calculate the posterior probability the average treatment effect is positive for infarct sizes between $e-4$ and e . If the probability is less than 40%, enrich by only including patients with infarct sizes $e-5$ or less. This rule is applied only one time per interim analysis.	To clarify that the enrichment rule for infarct size can only be applied once per interim analysis.
Appendix F 4.3 Interim Monitoring for Early Stopping for Predicted Success Page 8	<i>[No text in previous version]</i>	In order that the trial stop for expected success, the predictive probability of trial success must exceed the threshold described above, and the analogous predictive probability of trial success for a dichotomized version of the utility function must also exceed the same threshold. The dichotomized utility function is also discussed in Appendix B.	Updated expected success criteria to include success of dichotomous 90 day mRS analysis in addition to weighted mRS analysis. To be consistent with the final analysis to be provided to FDA upon study conclusion, this language was modified to include dichotomous analysis in addition to weighted mRS analysis.

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification
Appendix F Section 5.0 Example Trial Page 8	<p>In this section we present graphical descriptions of the data collected, analyses performed, and decisions made during the course of the trial. Our example is just one of the many simulated data sets and trials.</p>	<p>In this section we present graphical descriptions of the data collected, analyses performed, and decisions made during the course of the trial. Our example is just one of the many simulated data sets and trials.</p> <p>The example trial presented in this section was created using a slightly different, older version of the design, in which the dichotomized version of the utility function is not used in the expected success stopping decisions.</p>	<p>Updated simulations of study design to incorporate simultaneous dichotomous analysis of 90 day mRS in addition to weighted utility function analysis of 90 day mRS.</p>

Appendix F
Section 6.1 Type I Error
Page 18

Simulation	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
1	0.0149	0	498.0	0.006	0.002	0.002	0.001	0.004
2	0.0192	0	498.3	0.007	0.002	0.003	0.002	0.005
3	0.0227	0	496.7	0.007	0.001	0.003	0.002	0.009
4	0.0204	0	497.6	0.007	0.002	0.003	0.001	0.007
5	0.0242	0	496.0	0.007	0.002	0.003	0.002	0.010
6	0.0239	0	496.9	0.007	0.001	0.003	0.002	0.011
7	0.0211	0	497.1	0.006	0.003	0.004	0.002	0.006
8	0.0217	0	496.9	0.008	0.001	0.002	0.002	0.008
9	0.0239	0	496.7	0.007	0.002	0.004	0.003	0.009
10	0.0238	0	496.7	0.007	0.002	0.003	0.002	0.009
11	0.0240	0	496.8	0.011	0.002	0.004	0.002	0.007
12	0.0219	0.97	282.4	0.007	0.002	0.003	0.002	0.008
W/ futility								

Table 5: estimated Type I error probability for several scenarios.

Simulation	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
1	0.0136	0	499.4	0.004	0.002	0.002	0.001	0.005
2	0.0173	0	499.5	0.005	0.002	0.001	0.003	0.006
3	0.0194	0	498.4	0.005	0.004	0.001	0.002	0.007
4	0.0159	0	499.3	0.005	0.002	0.003	0.002	0.005
5	0.0171	0	498.4	0.005	0.004	0.001	0.002	0.005
6	0.0157	0	499.0	0.004	0.002	0.001	0.002	0.006
7	0.0151	0	499.0	0.005	0.002	0.002	0.002	0.004
8	0.0121	0	499.0	0.003	0.001	0.002	0.001	0.005
9	0.0162	0	498.4	0.005	0.003	0.002	0.002	0.004
10	0.0173	0	499.2	0.005	0.004	0.002	0.002	0.005
11	0.0160	0	499.3	0.004	0.002	0.003	0.003	0.004
12	0.0071	0.977	239.9	0.002	0.001	0.001	0.001	0.002
W/ futility								

Table 5: estimated Type I error probability for several scenarios.

Updated simulations of study design to incorporate simultaneous dichotomous analysis of 90 day mRS in addition to weighted utility function analysis of 90 day mRS.

In fact the Type I error probabilities for this design are conservative and well below the target value of 0.025. This is because the critical value (98.6%) for the design was selected using a previous version of the design, where the polychotomous utility function alone determined early stopping. Designs where early stopping decisions are based on criteria close to the primary analysis tend to inflate Type I error above the nominal value more than designs that use other criteria. Including the dichotomous utility function in early stopping decisions therefore reduces the Type I error probability.

The primary analysis in this trial uses the utility function defined in Table 1. However, it may still be of interest to evaluate the probability that, at the end of the trial, a version of the primary analysis using the dichotomized utility function would yield a significant result (98.6% or higher posterior probability that the device is beneficial). Estimated probabilities for the same null

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification																										
		<p>scenarios are shown in Table 5D below. These probabilities are, in all cases, smaller than the analogous probabilities for the polychotomous utility function.</p> <table border="1" data-bbox="1087 425 1404 882"> <thead> <tr> <th data-bbox="1087 425 1193 470">Simulation</th><th data-bbox="1193 425 1404 470">Probability of superiority</th></tr> </thead> <tbody> <tr><td data-bbox="1087 470 1193 507">1</td><td data-bbox="1193 470 1404 507">0.0122</td></tr> <tr><td data-bbox="1087 507 1193 545">2</td><td data-bbox="1193 507 1404 545">0.0154</td></tr> <tr><td data-bbox="1087 545 1193 582">3</td><td data-bbox="1193 545 1404 582">0.0187</td></tr> <tr><td data-bbox="1087 582 1193 620">4</td><td data-bbox="1193 582 1404 620">0.0129</td></tr> <tr><td data-bbox="1087 620 1193 657">5</td><td data-bbox="1193 620 1404 657">0.0150</td></tr> <tr><td data-bbox="1087 657 1193 695">6</td><td data-bbox="1193 657 1404 695">0.0129</td></tr> <tr><td data-bbox="1087 695 1193 732">7</td><td data-bbox="1193 695 1404 732">0.0136</td></tr> <tr><td data-bbox="1087 732 1193 770">8</td><td data-bbox="1193 732 1404 770">0.0099</td></tr> <tr><td data-bbox="1087 770 1193 807">9</td><td data-bbox="1193 770 1404 807">0.0135</td></tr> <tr><td data-bbox="1087 807 1193 845">10</td><td data-bbox="1193 807 1404 845">0.0147</td></tr> <tr><td data-bbox="1087 845 1193 882">11</td><td data-bbox="1193 845 1404 882">0.0139</td></tr> <tr><td data-bbox="1087 882 1193 904">12 (W/ futility)</td><td data-bbox="1193 882 1404 904">0.0043</td></tr> </tbody> </table> <p>Table 5D: estimated probability that the trial will demonstrate superiority with respect to the dichotomized utility function, using the form of the primary analysis with the utilities changed.</p>	Simulation	Probability of superiority	1	0.0122	2	0.0154	3	0.0187	4	0.0129	5	0.0150	6	0.0129	7	0.0136	8	0.0099	9	0.0135	10	0.0147	11	0.0139	12 (W/ futility)	0.0043	
Simulation	Probability of superiority																												
1	0.0122																												
2	0.0154																												
3	0.0187																												
4	0.0129																												
5	0.0150																												
6	0.0129																												
7	0.0136																												
8	0.0099																												
9	0.0135																												
10	0.0147																												
11	0.0139																												
12 (W/ futility)	0.0043																												

Appendix F
Section 6.2 Power
Page 21

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.015	0.979	288.4	0.01	0.00	0.00	0.00	0.01
0.50	0.273	0.676	376.1	0.08	0.02	0.06	0.02	0.09
0.75	0.618	0.326	381.6	0.16	0.04	0.16	0.04	0.22
1.0	0.858	0.108	343.6	0.19	0.04	0.23	0.08	0.44
1.25	0.979	0.010	287.8	0.14	0.04	0.18	0.07	0.56
1.50	0.995	0.002	249.2	0.10	0.03	0.18	0.07	0.62

Table 8: Operating characteristics for Simulation Set A, which features default profiles for accrual, infarct size distribution, mRS distributions, and longitudinal model.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.017	0.971	243.2	0.01	0.00	0.00	0.00	0.00
0.50	0.289	0.664	359.2	0.05	0.03	0.04	0.04	0.13
0.75	0.617	0.337	401.3	0.11	0.07	0.05	0.07	0.32
1.0	0.871	0.116	390.1	0.11	0.07	0.07	0.11	0.51
1.25	0.967	0.029	333.8	0.09	0.06	0.06	0.11	0.65
1.50	0.997	0.003	292.4	0.06	0.04	0.04	0.10	0.76

Table 8: Operating characteristics for Simulation Set A, which features default profiles for accrual, infarct size distribution, mRS distributions, and longitudinal model.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.014	0.980	297.4	0.01	0.00	0.00	0.00	0.00
0.50	0.303	0.642	384.9	0.09	0.02	0.08	0.02	0.09
0.75	0.590	0.349	393.3	0.18	0.03	0.13	0.05	0.20
1.0	0.859	0.106	365.5	0.18	0.05	0.20	0.06	0.37
1.25	0.967	0.019	319.2	0.15	0.05	0.22	0.07	0.48
1.50	0.996	0.004	271.3	0.12	0.03	0.19	0.06	0.60

Table 9: Operating characteristics for Simulation Set B, which features a faster accrual rate. Expected sample sizes are larger than in the default scenario.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.016	0.978	253.6	0.00	0.00	0.00	0.00	0.01
0.50	0.269	0.685	366.0	0.05	0.03	0.03	0.04	0.11
0.75	0.592	0.361	401.6	0.11	0.06	0.04	0.09	0.29
1.0	0.869	0.116	398.4	0.12	0.08	0.06	0.13	0.56
1.25	0.978	0.020	362.1	0.10	0.08	0.05	0.12	0.63
1.50	0.994	0.006	306.6	0.07	0.04	0.05	0.10	0.74

Table 9: Operating characteristics for Simulation Set B, which features a faster accrual rate. Expected sample sizes are larger than in the default scenario.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.021	0.974	283.5	0.01	0.00	0.00	0.00	0.01
0.50	0.303	0.654	365.2	0.09	0.03	0.06	0.02	0.11
0.75	0.644	0.299	366.4	0.17	0.04	0.14	0.06	0.25
1.0	0.855	0.116	325.7	0.17	0.05	0.17	0.07	0.41
1.25	0.974	0.017	267.4	0.12	0.04	0.18	0.07	0.56
1.50	0.998	0.002	225.4	0.08	0.02	0.15	0.07	0.68

Table 10: Operating characteristics for Simulation Set C, which features a relatively slow accrual rate. Successful trials are slightly more likely than in the default case, since early stopping for expected success decisions are made based on relatively more complete data. Sample sizes, however, tend to be smaller.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.018	0.974	243.6	0.00	0.00	0.00	0.00	0.01
0.50	0.292	0.661	359.0	0.05	0.04	0.04	0.02	0.14
0.75	0.616	0.352	382.6	0.11	0.06	0.05	0.06	0.33
1.0	0.880	0.102	368.0	0.10	0.08	0.07	0.11	0.53
1.25	0.978	0.021	321.6	0.07	0.06	0.06	0.11	0.67
1.50	0.994	0.006	264.5	0.05	0.04	0.03	0.09	0.79

Table 10: Operating characteristics for Simulation Set C, which features a relatively slow accrual rate. Successful trials are slightly more likely than in the default case, since early stopping for expected success decisions are made based on relatively more complete data. Sample sizes, however, tend to be smaller.

Updated simulations of study design to incorporate simultaneous dichotomous analysis of 90 day mRS in addition to weighted utility function analysis of 90 day mRS.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.020	0.974	302.2	0.00	0.00	0.00	0.00	0.01
0.50	0.402	0.539	399.0	0.12	0.03	0.06	0.03	0.14
0.75	0.801	0.156	379.2	0.22	0.08	0.21	0.07	0.36
1.0	0.947	0.040	320.7	0.20	0.05	0.21	0.05	0.44
1.25	0.995	0.001	263.3	0.13	0.03	0.18	0.07	0.59
1.50	1.000	0.000	219.2	0.07	0.02	0.12	0.06	0.73

Table 11: Operating characteristics for Simulation Set D, characterized by better mRS outcomes for given infarct sizes than the default profile. Successful trials are more common than in the default case, and large effects can be detected with fewer patients on the average. These findings likely depend on the specific choices for the infarct size and mRS distributions.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.032	0.962	255.6	0.01	0.00	0.00	0.01	0.01
0.50	0.372	0.580	382.8	0.09	0.05	0.03	0.03	0.17
0.75	0.729	0.236	401.8	0.16	0.10	0.07	0.08	0.32
1.0	0.942	0.047	365.4	0.13	0.10	0.07	0.10	0.55
1.25	0.994	0.003	301.4	0.09	0.08	0.06	0.10	0.68
1.50	0.998	0.001	246.8	0.04	0.04	0.04	0.09	0.80

Table 11: Operating characteristics for Simulation Set D, characterized by better mRS outcomes for given infarct sizes than the default profile. Successful trials are more common than in the default case, and large effects can be detected with fewer patients on the average. These findings likely depend on the specific choices for the infarct size and mRS distributions. The 0.032 probability for the null scenario is a random high in simulation results; there is almost a 10% chance of 32 or more successes out of 1000 trials with success probability 0.025.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.016	0.977	291.0	0.01	0.00	0.00	0.00	0.00
0.50	0.254	0.691	389.1	0.08	0.03	0.05	0.03	0.07
0.75	0.568	0.368	399.7	0.16	0.06	0.14	0.04	0.18
1.0	0.849	0.126	375.2	0.18	0.06	0.22	0.06	0.34
1.25	0.968	0.026	329.1	0.17	0.05	0.23	0.08	0.44
1.50	0.994	0.005	286.4	0.16	0.03	0.21	0.06	0.54

Table 12: Operating characteristics for Simulation Set E, which is characterized by worse mRS outcomes for given infarct sizes than in the default profile. In general this scenario is slightly unfavorable to the default scenario in operating characteristics.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.020	0.972	280.3	0.01	0.00	0.00	0.00	0.01
0.50	0.295	0.655	373.0	0.08	0.02	0.07	0.03	0.09
0.75	0.578	0.365	380.6	0.14	0.04	0.13	0.06	0.21
1.0	0.823	0.148	345.3	0.15	0.03	0.19	0.08	0.37
1.25	0.965	0.026	298.0	0.12	0.03	0.22	0.07	0.53
1.50	0.990	0.006	247.4	0.08	0.02	0.13	0.10	0.66

Table 12: Operating characteristics for Simulation Set E, which is characterized by worse mRS outcomes for given infarct sizes than in the default profile. In general this scenario is slightly unfavorable to the default scenario in operating characteristics.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.020	0.973	290.3	0.01	0.00	0.00	0.00	0.01
0.50	0.311	0.639	373.0	0.10	0.02	0.06	0.02	0.11
0.75	0.635	0.302	369.7	0.16	0.04	0.13	0.05	0.26
1.0	0.864	0.105	315.5	0.15	0.06	0.16	0.05	0.44
1.25	0.985	0.010	267.8	0.13	0.04	0.19	0.09	0.54
1.50	0.995	0.002	224.6	0.07	0.03	0.14	0.08	0.69

Table 13: Operating characteristics for Simulation Set F, in which 30-day mRS scores are always identical to 90-day mRS scores. Since more information is available earlier, decisions to stop early for expected success are more successful, so that win probabilities are slightly larger and expected sample sizes are smaller.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.016	0.977	291.0	0.01	0.00	0.00	0.00	0.00
0.50	0.254	0.691	389.1	0.08	0.03	0.05	0.03	0.07
0.75	0.568	0.368	399.7	0.16	0.06	0.14	0.04	0.18
1.0	0.849	0.126	375.2	0.18	0.06	0.22	0.06	0.34
1.25	0.968	0.026	329.1	0.17	0.05	0.23	0.08	0.44
1.50	0.994	0.005	286.4	0.16	0.03	0.21	0.06	0.54

Table 14: Operating characteristics for Simulation Set G, in which 30-day mRS scores are nearly unrelated to 90-day mRS scores. Win probabilities are generally decreased and expected sample sizes increased.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.015	0.979	245.2	0.00	0.00	0.00	0.00	0.01
0.50	0.315	0.630	362.6	0.06	0.03	0.04	0.04	0.14
0.75	0.640	0.325	388.4	0.09	0.07	0.05	0.08	0.35
1.0	0.876	0.103	365.2	0.12	0.07	0.08	0.11	0.50
1.25	0.970	0.027	309.5	0.08	0.05	0.05	0.10	0.68
1.50	0.994	0.004	258.5	0.06	0.03	0.05	0.08	0.78

Table 13: Operating characteristics for Simulation Set F, in which 30-day mRS scores are always identical to 90-day mRS scores. Since more information is available earlier, decisions to stop early for expected success are more successful, so that win probabilities are slightly larger and expected sample sizes are smaller.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.012	0.985	241.8	0.00	0.00	0.00	0.00	0.01
0.50	0.255	0.698	362.4	0.06	0.03	0.03	0.03	0.10
0.75	0.592	0.362	405.3	0.09	0.06	0.04	0.10	0.28
1.0	0.848	0.131	400.0	0.12	0.07	0.06	0.11	0.49
1.25	0.959	0.035	372.4	0.13	0.08	0.07	0.12	0.56
1.50	0.992	0.008	321.0	0.08	0.06	0.05	0.10	0.71

Table 14: Operating characteristics for Simulation Set G, in which 30-day mRS scores are nearly unrelated to 90-day mRS scores. Win probabilities are generally decreased and expected sample sizes increased.

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.021	0.967	300.3	0.00	0.00	0.00	0.00	0.01
0.50	0.292	0.638	379.5	0.06	0.02	0.06	0.03	0.12
0.75	0.616	0.312	386.6	0.13	0.04	0.12	0.05	0.27
1.0	0.852	0.108	345.4	0.12	0.03	0.18	0.07	0.45
1.25	0.959	0.020	298.7	0.11	0.03	0.15	0.08	0.59
1.50	0.993	0.005	247.2	0.07	0.01	0.13	0.05	0.74

Table 15: Operating characteristics for Simulation Set H, in which each infarct size between 0 and 50 is equally likely. This

Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.014	0.981	256.6	0.00	0.00	0.00	0.00	0.01
0.50	0.260	0.691	368.6	0.05	0.05	0.02	0.04	0.11
0.75	0.563	0.365	405.6	0.09	0.08	0.06	0.05	0.30
1.0	0.860	0.108	397.8	0.12	0.10	0.07	0.09	0.49
1.25	0.967	0.026	347.2	0.08	0.06	0.05	0.08	0.67
1.50	0.990	0.008	295.6	0.05	0.05	0.04	0.06	0.79

Table 15: Operating characteristics for Simulation Set H, in which each infarct size between 0 and 50 is equally likely. This

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification																																																																																																																																								
	<p>change in assumptions does not have a dramatic effect on power, but enrichment is less likely and the full subpopulation is more likely to be chosen by the design.</p> <table border="1" data-bbox="477 425 977 654"> <thead> <tr> <th rowspan="2">Effect</th><th rowspan="2">P(Win)</th><th rowspan="2">Pr(Fut)</th><th rowspan="2">Mean SS</th><th colspan="5">Final Infarct Size and Winning Trial</th></tr> <tr> <th>0-30</th><th>0-35</th><th>0-40</th><th>0-45</th><th>0-50</th></tr> </thead> <tbody> <tr> <td>0</td><td>0.018</td><td>0.978</td><td>281.5</td><td>0.01</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td></tr> <tr> <td>0.50</td><td>0.313</td><td>0.645</td><td>378.5</td><td>0.12</td><td>0.03</td><td>0.05</td><td>0.03</td><td>0.08</td></tr> <tr> <td>0.75</td><td>0.659</td><td>0.301</td><td>384.7</td><td>0.22</td><td>0.07</td><td>0.16</td><td>0.04</td><td>0.18</td></tr> <tr> <td>1.0</td><td>0.896</td><td>0.088</td><td>347.3</td><td>0.28</td><td>0.06</td><td>0.22</td><td>0.06</td><td>0.29</td></tr> <tr> <td>1.25</td><td>0.981</td><td>0.014</td><td>289.8</td><td>0.22</td><td>0.08</td><td>0.24</td><td>0.05</td><td>0.39</td></tr> <tr> <td>1.50</td><td>0.998</td><td>0.002</td><td>250.8</td><td>0.14</td><td>0.05</td><td>0.27</td><td>0.06</td><td>0.48</td></tr> </tbody> </table> <p>Table 16: Operating characteristics for Simulation Set I, in which infarcts tend to be smaller than in the default profile. This change in assumptions makes it relatively easier to detect a device effect, and smaller subpopulations are more likely to be chosen by the design.</p>	Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial					0-30	0-35	0-40	0-45	0-50	0	0.018	0.978	281.5	0.01	0.00	0.00	0.00	0.00	0.50	0.313	0.645	378.5	0.12	0.03	0.05	0.03	0.08	0.75	0.659	0.301	384.7	0.22	0.07	0.16	0.04	0.18	1.0	0.896	0.088	347.3	0.28	0.06	0.22	0.06	0.29	1.25	0.981	0.014	289.8	0.22	0.08	0.24	0.05	0.39	1.50	0.998	0.002	250.8	0.14	0.05	0.27	0.06	0.48	<p>change in assumptions does not have a dramatic effect on power, but enrichment is less likely and the full subpopulation is more likely to be chosen by the design.</p> <table border="1" data-bbox="998 425 1499 654"> <thead> <tr> <th rowspan="2">Effect</th><th rowspan="2">P(Win)</th><th rowspan="2">Pr(Fut)</th><th rowspan="2">Mean SS</th><th colspan="5">Final Infarct Size and Winning Trial</th></tr> <tr> <th>0-30</th><th>0-35</th><th>0-40</th><th>0-45</th><th>0-50</th></tr> </thead> <tbody> <tr> <td>0</td><td>0.014</td><td>0.979</td><td>239.6</td><td>0.01</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td></tr> <tr> <td>0.50</td><td>0.291</td><td>0.668</td><td>351.8</td><td>0.05</td><td>0.02</td><td>0.04</td><td>0.04</td><td>0.14</td></tr> <tr> <td>0.75</td><td>0.624</td><td>0.354</td><td>384.7</td><td>0.09</td><td>0.05</td><td>0.09</td><td>0.10</td><td>0.29</td></tr> <tr> <td>1.0</td><td>0.874</td><td>0.112</td><td>374.6</td><td>0.09</td><td>0.06</td><td>0.10</td><td>0.13</td><td>0.49</td></tr> <tr> <td>1.25</td><td>0.981</td><td>0.021</td><td>335.3</td><td>0.09</td><td>0.06</td><td>0.10</td><td>0.16</td><td>0.57</td></tr> <tr> <td>1.50</td><td>0.996</td><td>0.004</td><td>282.4</td><td>0.05</td><td>0.03</td><td>0.08</td><td>0.16</td><td>0.68</td></tr> </tbody> </table> <p>Table 16: Operating characteristics for Simulation Set I, in which infarcts tend to be smaller than in the default profile. This change in assumptions makes it relatively easier to detect a device effect, and smaller subpopulations are more likely to be chosen by the design.</p>	Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial					0-30	0-35	0-40	0-45	0-50	0	0.014	0.979	239.6	0.01	0.00	0.00	0.00	0.00	0.50	0.291	0.668	351.8	0.05	0.02	0.04	0.04	0.14	0.75	0.624	0.354	384.7	0.09	0.05	0.09	0.10	0.29	1.0	0.874	0.112	374.6	0.09	0.06	0.10	0.13	0.49	1.25	0.981	0.021	335.3	0.09	0.06	0.10	0.16	0.57	1.50	0.996	0.004	282.4	0.05	0.03	0.08	0.16	0.68	
Effect	P(Win)					Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial																																																																																																																																			
		0-30	0-35	0-40	0-45			0-50																																																																																																																																			
0	0.018	0.978	281.5	0.01	0.00	0.00	0.00	0.00																																																																																																																																			
0.50	0.313	0.645	378.5	0.12	0.03	0.05	0.03	0.08																																																																																																																																			
0.75	0.659	0.301	384.7	0.22	0.07	0.16	0.04	0.18																																																																																																																																			
1.0	0.896	0.088	347.3	0.28	0.06	0.22	0.06	0.29																																																																																																																																			
1.25	0.981	0.014	289.8	0.22	0.08	0.24	0.05	0.39																																																																																																																																			
1.50	0.998	0.002	250.8	0.14	0.05	0.27	0.06	0.48																																																																																																																																			
Effect	P(Win)	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial																																																																																																																																							
				0-30	0-35	0-40	0-45	0-50																																																																																																																																			
0	0.014	0.979	239.6	0.01	0.00	0.00	0.00	0.00																																																																																																																																			
0.50	0.291	0.668	351.8	0.05	0.02	0.04	0.04	0.14																																																																																																																																			
0.75	0.624	0.354	384.7	0.09	0.05	0.09	0.10	0.29																																																																																																																																			
1.0	0.874	0.112	374.6	0.09	0.06	0.10	0.13	0.49																																																																																																																																			
1.25	0.981	0.021	335.3	0.09	0.06	0.10	0.16	0.57																																																																																																																																			
1.50	0.996	0.004	282.4	0.05	0.03	0.08	0.16	0.68																																																																																																																																			

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)										Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)										Justification for Modification																																																																																																																																																																																																																																
Appendix F Section 6.3 Population Enrichment Page 27	<table border="1"> <thead> <tr> <th rowspan="2">Simulation Effect</th> <th rowspan="2">P(Win)</th> <th colspan="5">Final Infarct Size</th> <th colspan="5">Final Infarct Size and Winning Trial</th> </tr> <tr> <th>0-30</th><th>0-35</th><th>0-40</th><th>0-45</th><th>0-50</th> <th>0-30</th><th>0-35</th><th>0-40</th><th>0-45</th><th>0-50</th> </tr> </thead> <tbody> <tr> <td>E1</td><td>0.865</td><td>0.20</td><td>0.06</td><td>0.25</td><td>0.09</td><td>0.40</td><td>0.16</td><td>0.05</td><td>0.20</td><td>0.08</td><td>0.38</td> </tr> <tr> <td>E2</td><td>0.860</td><td>0.27</td><td>0.10</td><td>0.24</td><td>0.12</td><td>0.28</td><td>0.22</td><td>0.08</td><td>0.20</td><td>0.11</td><td>0.26</td> </tr> <tr> <td>E3</td><td>0.833</td><td>0.33</td><td>0.10</td><td>0.25</td><td>0.13</td><td>0.19</td><td>0.26</td><td>0.08</td><td>0.21</td><td>0.12</td><td>0.17</td> </tr> <tr> <td>E4</td><td>0.822</td><td>0.44</td><td>0.13</td><td>0.19</td><td>0.07</td><td>0.17</td><td>0.35</td><td>0.11</td><td>0.15</td><td>0.06</td><td>0.15</td> </tr> <tr> <td>E5</td><td>0.807</td><td>0.54</td><td>0.13</td><td>0.16</td><td>0.05</td><td>0.13</td><td>0.44</td><td>0.10</td><td>0.12</td><td>0.04</td><td>0.11</td> </tr> <tr> <td>E6</td><td>0.994</td><td>0.20</td><td>0.06</td><td>0.23</td><td>0.11</td><td>0.41</td><td>0.20</td><td>0.06</td><td>0.23</td><td>0.11</td><td>0.41</td> </tr> <tr> <td>E7</td><td>0.959</td><td>0.29</td><td>0.11</td><td>0.23</td><td>0.11</td><td>0.26</td><td>0.28</td><td>0.10</td><td>0.22</td><td>0.11</td><td>0.25</td> </tr> </tbody> </table>											Simulation Effect	P(Win)	Final Infarct Size					Final Infarct Size and Winning Trial					0-30	0-35	0-40	0-45	0-50	0-30	0-35	0-40	0-45	0-50	E1	0.865	0.20	0.06	0.25	0.09	0.40	0.16	0.05	0.20	0.08	0.38	E2	0.860	0.27	0.10	0.24	0.12	0.28	0.22	0.08	0.20	0.11	0.26	E3	0.833	0.33	0.10	0.25	0.13	0.19	0.26	0.08	0.21	0.12	0.17	E4	0.822	0.44	0.13	0.19	0.07	0.17	0.35	0.11	0.15	0.06	0.15	E5	0.807	0.54	0.13	0.16	0.05	0.13	0.44	0.10	0.12	0.04	0.11	E6	0.994	0.20	0.06	0.23	0.11	0.41	0.20	0.06	0.23	0.11	0.41	E7	0.959	0.29	0.11	0.23	0.11	0.26	0.28	0.10	0.22	0.11	0.25	<table border="1"> <thead> <tr> <th rowspan="2">Simulation Effect</th> <th rowspan="2">P(Win)</th> <th colspan="5">Final Infarct Size</th> <th colspan="5">Final Infarct Size and Winning Trial</th> </tr> <tr> <th>0-30</th><th>0-35</th><th>0-40</th><th>0-45</th><th>0-50</th> <th>0-30</th><th>0-35</th><th>0-40</th><th>0-45</th><th>0-50</th> </tr> </thead> <tbody> <tr> <td>E1</td><td>0.871</td><td>0.14</td><td>0.08</td><td>0.07</td><td>0.13</td><td>0.58</td><td>0.11</td><td>0.07</td><td>0.07</td><td>0.11</td><td>0.51</td> </tr> <tr> <td>E2</td><td>0.844</td><td>0.16</td><td>0.11</td><td>0.12</td><td>0.20</td><td>0.41</td><td>0.12</td><td>0.09</td><td>0.11</td><td>0.19</td><td>0.35</td> </tr> <tr> <td>E3</td><td>0.827</td><td>0.20</td><td>0.15</td><td>0.19</td><td>0.16</td><td>0.30</td><td>0.16</td><td>0.13</td><td>0.17</td><td>0.15</td><td>0.22</td> </tr> <tr> <td>E4</td><td>0.807</td><td>0.25</td><td>0.27</td><td>0.13</td><td>0.11</td><td>0.24</td><td>0.20</td><td>0.24</td><td>0.12</td><td>0.09</td><td>0.16</td> </tr> <tr> <td>E5</td><td>0.793</td><td>0.38</td><td>0.20</td><td>0.11</td><td>0.09</td><td>0.22</td><td>0.32</td><td>0.17</td><td>0.09</td><td>0.07</td><td>0.14</td> </tr> <tr> <td>E6</td><td>0.992</td><td>0.11</td><td>0.09</td><td>0.12</td><td>0.19</td><td>0.49</td><td>0.11</td><td>0.09</td><td>0.12</td><td>0.19</td><td>0.49</td> </tr> <tr> <td>E7</td><td>0.955</td><td>0.16</td><td>0.14</td><td>0.17</td><td>0.18</td><td>0.33</td><td>0.15</td><td>0.15</td><td>0.17</td><td>0.18</td><td>0.31</td> </tr> </tbody> </table>											Simulation Effect	P(Win)	Final Infarct Size					Final Infarct Size and Winning Trial					0-30	0-35	0-40	0-45	0-50	0-30	0-35	0-40	0-45	0-50	E1	0.871	0.14	0.08	0.07	0.13	0.58	0.11	0.07	0.07	0.11	0.51	E2	0.844	0.16	0.11	0.12	0.20	0.41	0.12	0.09	0.11	0.19	0.35	E3	0.827	0.20	0.15	0.19	0.16	0.30	0.16	0.13	0.17	0.15	0.22	E4	0.807	0.25	0.27	0.13	0.11	0.24	0.20	0.24	0.12	0.09	0.16	E5	0.793	0.38	0.20	0.11	0.09	0.22	0.32	0.17	0.09	0.07	0.14	E6	0.992	0.11	0.09	0.12	0.19	0.49	0.11	0.09	0.12	0.19	0.49	E7	0.955	0.16	0.14	0.17	0.18	0.33	0.15	0.15	0.17	0.18	0.31	<p>Updated simulations of study design to incorporate simultaneous dichotomous analysis of 90 day mRS in addition to weighted utility function analysis of 90 day mRS.</p>										
Simulation Effect	P(Win)	Final Infarct Size					Final Infarct Size and Winning Trial																																																																																																																																																																																																																																														
		0-30	0-35	0-40	0-45	0-50	0-30	0-35	0-40	0-45	0-50																																																																																																																																																																																																																																										
E1	0.865	0.20	0.06	0.25	0.09	0.40	0.16	0.05	0.20	0.08	0.38																																																																																																																																																																																																																																										
E2	0.860	0.27	0.10	0.24	0.12	0.28	0.22	0.08	0.20	0.11	0.26																																																																																																																																																																																																																																										
E3	0.833	0.33	0.10	0.25	0.13	0.19	0.26	0.08	0.21	0.12	0.17																																																																																																																																																																																																																																										
E4	0.822	0.44	0.13	0.19	0.07	0.17	0.35	0.11	0.15	0.06	0.15																																																																																																																																																																																																																																										
E5	0.807	0.54	0.13	0.16	0.05	0.13	0.44	0.10	0.12	0.04	0.11																																																																																																																																																																																																																																										
E6	0.994	0.20	0.06	0.23	0.11	0.41	0.20	0.06	0.23	0.11	0.41																																																																																																																																																																																																																																										
E7	0.959	0.29	0.11	0.23	0.11	0.26	0.28	0.10	0.22	0.11	0.25																																																																																																																																																																																																																																										
Simulation Effect	P(Win)	Final Infarct Size					Final Infarct Size and Winning Trial																																																																																																																																																																																																																																														
		0-30	0-35	0-40	0-45	0-50	0-30	0-35	0-40	0-45	0-50																																																																																																																																																																																																																																										
E1	0.871	0.14	0.08	0.07	0.13	0.58	0.11	0.07	0.07	0.11	0.51																																																																																																																																																																																																																																										
E2	0.844	0.16	0.11	0.12	0.20	0.41	0.12	0.09	0.11	0.19	0.35																																																																																																																																																																																																																																										
E3	0.827	0.20	0.15	0.19	0.16	0.30	0.16	0.13	0.17	0.15	0.22																																																																																																																																																																																																																																										
E4	0.807	0.25	0.27	0.13	0.11	0.24	0.20	0.24	0.12	0.09	0.16																																																																																																																																																																																																																																										
E5	0.793	0.38	0.20	0.11	0.09	0.22	0.32	0.17	0.09	0.07	0.14																																																																																																																																																																																																																																										
E6	0.992	0.11	0.09	0.12	0.19	0.49	0.11	0.09	0.12	0.19	0.49																																																																																																																																																																																																																																										
E7	0.955	0.16	0.14	0.17	0.18	0.33	0.15	0.15	0.17	0.18	0.31																																																																																																																																																																																																																																										

Table 18: power and enrichment decisions when the truth is that the benefit of the device depends on infarct size. For each scenario, we present the total probability of a successful trial in the P(Win) column. We then present the probability that the design selects each of the five possible subpopulations regardless of whether the trial is successful, and finally the probability that a trial is successful and chooses each of the five possible subpopulations.

Table 18: power and enrichment decisions when the truth is that the benefit of the device depends on infarct size. For each scenario, we present the total probability of a successful trial in the P(Win) column. We then present the probability that the design selects each of the five possible subpopulations regardless of whether the trial is successful, and finally the probability that a trial is successful and chooses each of the five possible subpopulations.

Appendix F
Section 6.4 Probability of successful final analysis with dichotomized utility
Page 28

[No text in previous version]

6.4 Probability of successful final analysis with dichotomized utility

We can also evaluate the probability of a significant result when the final data are analyzed using the dichotomized utility function. For brevity, we focus on the scenarios in Simulation Set A of Section 6.2, so the numbers in Table 19 can be compared to those in Table 8.

Effect	P(Win)*	Pr(Fut)	Mean SS	Final Infarct Size and Winning Trial				
				0-30	0-35	0-40	0-45	0-50
0	0.009	0.971	243.2	0.01	0.00	0.00	0.00	0.00
0.50	0.174	0.664	359.2	0.05	0.03	0.04	0.04	0.13
0.75	0.447	0.337	401.3	0.11	0.07	0.05	0.07	0.32
1.0	0.681	0.116	390.1	0.11	0.07	0.07	0.11	0.51
1.25	0.902	0.029	333.8	0.09	0.06	0.06	0.11	0.65
1.50	0.980	0.003	292.4	0.06	0.04	0.04	0.10	0.76

Table 19: Operating characteristics for Simulation Set A, which features default profiles for accrual, infarct size distribution, mRS distributions, and longitudinal model. The numbers in the P(Win)* column refer to analyses performed on the final data using the dichotomized utility function. The other numbers are reproduced from Table 8. Probabilities of significant results for the dichotomous analysis are considerably smaller than for the primary analysis (which uses the utility function in Table 1). The utility analysis is a more sensitive method of detecting a benefit. Dichotomizing the endpoint has the effect of maximizing the variance of the endpoint as a function of its mean. In the case of Simulation Set A, the estimated standard deviations of outcomes are about 50% larger for the dichotomized analysis than they are for the utility analysis, so loss of power is inevitable.

Updated simulations of study design to incorporate simultaneous dichotomous analysis of 90 day mRS in addition to weighted utility function analysis of 90 day mRS.

Section of Protocol Modified	Existing Text as Written in Protocol: (CDM10000146, 28 April 2016 Rev: AC)	Revised/New Text as Written in Protocol (CDM10000146, 26 Jan 2017 Rev: AD)	Justification for Modification																																								
Appendix F Appendix B: Statistical Model for Futility and Expected Success Analyses Page 33	<i>[No text in previous version]</i>	<p>Also used in the decisions to stop for expected success is a slight modification of this predictive probability. We replace the primary utility function with a dichotomized version (as in Table 1A below) and then calculate the expected success predictive probability using the dichotomous utility function. (We first re-analyze the available data using the model in Appendix A and the dichotomized endpoint values, and then use this model to predict future data with dichotomized endpoint values.) For the trial to stop for expected success, the predictive probability must exceed the threshold for both the primary utility function and the dichotomized utility function.</p> <table border="1" data-bbox="994 736 1495 856"> <thead> <tr> <th>mRS</th> <th>0</th> <th>1</th> <th>2</th> <th>3</th> <th>4</th> <th>5</th> <th>6</th> </tr> </thead> <tbody> <tr> <td>Rivero-Arias et al</td> <td>10</td> <td>8.7</td> <td>7.3</td> <td>6.0</td> <td>2.8</td> <td>-0.1</td> <td>0</td> </tr> <tr> <td>Hong & Saver</td> <td>10</td> <td>9.5</td> <td>7.9</td> <td>6.7</td> <td>3.5</td> <td>0.1</td> <td>0</td> </tr> <tr> <td>This Trial</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> <tr> <td>Dichotomized</td> <td>10</td> <td>10</td> <td>10</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> </tbody> </table> <p>Table 1A: dichotomized utility function used in expected success predictive probability calculations.</p>	mRS	0	1	2	3	4	5	6	Rivero-Arias et al	10	8.7	7.3	6.0	2.8	-0.1	0	Hong & Saver	10	9.5	7.9	6.7	3.5	0.1	0	This Trial	10	9.1	7.6	6.5	3.3	0	0	Dichotomized	10	10	10	0	0	0	0	Updated simulations of study design to incorporate simultaneous dichotomous analysis of 90 day mRS in addition to weighted utility function analysis of 90 day mRS.
mRS	0	1	2	3	4	5	6																																				
Rivero-Arias et al	10	8.7	7.3	6.0	2.8	-0.1	0																																				
Hong & Saver	10	9.5	7.9	6.7	3.5	0.1	0																																				
This Trial	10	9.1	7.6	6.5	3.3	0	0																																				
Dichotomized	10	10	10	0	0	0	0																																				

Statistical Analysis Plan

DAWN Trial

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

Updated Date: 04JUN2014

Concentric Medical, a business unit of Stryker Neurovascular
Fremont, CA USA

THESE DOCUMENTS ARE THE PROPERTY OF STRYKER NEUROVASCULAR AND SHALL NOT BE REPRODUCED,
DISTRIBUTED, DISCLOSED OR USED FOR MANUFACTURE OR SALE OF APPARATUS WITHOUT THE EXPRESS WRITTEN
CONSENT OF STRYKER NEUROVASCULAR.

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 1 of 24

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	3
1. PROTOCOL SUMMARY	7
2. STUDY OBJECTIVES	7
2.1. PRIMARY OBJECTIVE	7
2.2. SECONDARY OBJECTIVE	7
3. STUDY DESIGN	7
3.1. STUDY ENDPOINTS	8
3.1.1. PRIMARY ENDPOINT	8
3.1.2. SECONDARY ENDPOINTS	8
3.1.3. PRIMARY SAFETY OUTCOME	8
3.1.4. SECONDARY SAFETY OUTCOME	8
3.2. RANDOMIZATION	9
4. STATISTICAL METHODS	9
4.1. PRIMARY STATISTICAL NULL HYPOTHESIS	9
4.2. THE SECONDARY EFFICACY AND SAFETY ENDPOINTS	10
4.3. SAMPLE SIZE ESTIMATE AND JUSTIFICATION	10
4.4. CONTROL OF SYSTEMATIC ERROR/BIAS	11
4.5. ELIGIBILITY OF SUBJECTS, EXCLUSIONS, AND MISSING DATA	11
4.6. POPULATION DEFINITIONS	11
4.7. ANALYSIS POPULATIONS	12
4.8. ESTIMATED DURATION OF SUBJECT PARTICIPATION	12
4.9. ANALYSES SCHEDULE	13
4.10. INTERIM ANALYSIS	14
4.10.1. INTERIM MONITORING FOR EARLY FUTILITY	14
4.10.2. ENRICHMENT	14
4.10.3. INTERIM MONITORING FOR EXPECTED SUCCESS	15
4.10.4. LONGITUDINAL MODEL	15
4.11. EFFICACY ANALYSES	15
4.11.1. SUBJECT ACCOUNTABILITY	16
4.11.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS	16
4.11.3. CLINICAL EVALUATION	17
4.11.4. STUDY DEVICE ACCOUNTABILITY	17
4.11.5. ANALYSIS OF PRIMARY EFFECTIVENESS ENDPOINTS	17
4.11.6. ANALYSIS OF SECONDARY EFFECTIVENESS ENDPOINTS	17
4.11.7. POOLING ACROSS SITES	18
4.11.8. OTHER PRE-PLANNED ANALYSIS	19
4.11.9. HEALTHY ECONOMIC EVALUATION	19
4.12. SAFETY ANALYSIS	19
4.12.1. ADVERSE EVENTS	19
4.12.2. SUMMARIES OF ADVERSE EVENTS	21
4.12.3. ANALYSIS OF PRIMARY SAFETY ENDPOINTS	21
4.12.4. ANALYSIS OF SECONDARY SAFETY OUTCOME	21
5. PROGRAMMING CONSIDERATIONS	22
5.1. STATISTICAL SOFTWARE	22
5.2. METHODS FOR HANDLING MISSING DATA ESPECIALLY THE AE START DATE	22
5.3. RULES FOR CALCULATING RATES AND HANDLING DENOMINATORS	23
6. STATISTICAL REPORT TEMPLATE	23
7. REFERENCES	24

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 2 of 24

List of Abbreviations and Definition of Terms

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
DBP	Diastolic Blood Pressure
DE	Distal Embolization
DMC	Data Monitoring Committee
DNR	Do Not Resuscitate

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 3 of 24

Abbreviation	Full Term
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
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

Concentric Medical, a business unit of Stryker Neurovascular
 DAWN Trial Statistical Analysis Plan
 CDM10000704, Ver. AA
 Page 4 of 24

Abbreviation	Full Term
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
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

Concentric Medical, a business unit of Stryker Neurovascular
 DAWN Trial Statistical Analysis Plan
 CDM10000704, Ver. AA
 Page 5 of 24

Abbreviation	Full Term
SAH	Subarachnoid Hemorrhage
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

Concentric Medical, a business unit of Stryker Neurovascular
 DAWN Trial Statistical Analysis Plan
 CDM10000704, Ver. AA
 Page 6 of 24

1. PROTOCOL SUMMARY

OVERVIEW AND INVESTIGATIONAL PLAN

This document contains a detailed description of the Statistical Analysis Plan (SAP) for the data from the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention (DAWN).

It provides specifications for the statistical analyses of the data to be prepared and presented for the purpose of demonstrating efficacy and safety to fulfill Food and Drug Administration (FDA) IDE requirements.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA. This plan may be revised during the study to accommodate any study plan change request by FDA, to make changes to adapt to unexpected issues in study execution or data that affects planned analyses. The final plan will be issued prior to final data lock. Furthermore, as no analysis plan prepared in advance of the data can be definitive, the final report may contain additional tables, footnotes or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final report.

2. STUDY OBJECTIVES

2.1. 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.

2.2. 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.

3. STUDY DESIGN

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.

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 7 of 24

Up to a total of 50 worldwide sites with <= 20 sites outside of the U.S will participate in the study. A maximum of 500 subjects is planned to be enrolled; 250 in the Treatment arm and 250 in the Control arm over an approximate 36-month recruitment period. Total study duration will be approximately 39 months (+/- 9 months), including one 24 (-6/+24) hours' MRI/MRA or CT/CTA and NIHSS assessment followed by Day 5-7, 30 (\pm 14), and Day 90 (\pm 14) clinical assessments.

3.1. Study Endpoints

3.1.1. Primary Endpoint

The primary endpoint is a comparison of the difference between the average weighted modified Rankin Scale score at 90 days post randomization between the two arms. 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. [46-47]of Protocol.

3.1.2. Secondary Endpoints

Both Arms:

1. Proportion of subjects with a good functional outcome at 90 days, defined as mRS \leq 2
2. Proportion of subjects with "early response" at Day 5-7/Discharge (whichever is earlier), defined as a NIHSS drop of \geq 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.

Treatment Arm Only:

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

3.1.3. Primary Safety Outcome

Both Arms:

1. Incidence of stroke-related mortality at 90 days

3.1.4. Secondary Safety Outcomes

Both Arms:

- a. Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero)
- b. Incidence of neurological deterioration from baseline NIHSS score through Day 5-7/discharge (whichever is earlier) post randomization (time zero). Neurological

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 8 of 24

deterioration is defined as ≥ 4 point increase in the NIHSS score from the baseline score.

Treatment Arm:

- c. 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

3.2. Randomization

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). Blocks will be assigned to all sites including the stratification mapping to maintain balance at all sites.

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.

4. STATISTICAL METHODS

4.1. Primary Statistical Null Hypothesis

The null hypothesis is that there is no difference in the average of the weighted mRS categories at 90 days in the Trevo Thrombectomy plus Medical Management group compared to Medical Management alone.

The alternative hypothesis is that 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 primary endpoint analysis is a Bayesian analysis of the weighted 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.

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 9 of 24

Enrichment decisions and early stopping rules are based on Bayesian predictive probabilities outlined in the Adaptive Design Plan in Appendix F of Study Protocol.

4.2. The Secondary efficacy and safety endpoints.

For binary outcomes, the count and percentage will be provided for each treatment arm. The difference in the rate between the treatment arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test as appropriate. Fisher's exact test is used in place of the Chi-square test when at least one cell count in the 2x2 table has expected value less than 5 or total number of sample $N \leq 40$.

The p value will be denoted with an asterisk (*) in the case where a Fisher's exact test was used.

Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

$$SE = \sqrt{\{(1-p_1)/n_{11} + (1-p_2)/n_{21}\}}$$

$$95\% \text{ CI} = RR \cdot \exp(\pm 1.96 \cdot SE)$$

For continuous outcomes, n, mean, median, interquartile (Q3-Q1), standard deviation, minimum, and maximum will be provided for each treatment arm. P-values will be calculated with t-test assuming un-equal variances to compare the difference between two treatment arms.

Difference = Trevo thrombectomy plus medical management – medical management.

$$95\% \text{ CI} = \text{Diff} \pm 1.96 \cdot SE$$

$$SE = \sqrt{p_1 q_1 / n_1 + p_2 q_2 / n_2} \text{ for proportions,}$$

$$SE = \sqrt{[(1/n_1 + 1/n_2) \{(n_1-1)s_1^2 + (n_2-1)s_2^2\} / (N-2)]} \text{ for continuous variables.}$$

For ordinal variable, Wilcoxon rank sum test will be used and footnoted.

4.3. 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 \geq 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 1**.

Table1. 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

4.4. 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.

4.5. 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 of study protocol.

4.6. 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 RAPID 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.

4.7. 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 of study protocol). 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.

4.8. Estimated Duration of Subject Participation

Subjects will be followed for 90 (± 14) days post-procedure, with data collection 24(-6/+24) hours post randomization, on the day of hospital discharge or 5 to 7 days (whichever occurred

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 12 of 24

sooner), 30 days (± 14 days), and 90 days (± 14 days) post-procedure. Subjects who do not withdraw prematurely from the study will be followed for a maximum of 104 days following the study procedure. Any subject who discontinues from the study for any reason will be followed to monitor safety for the duration of the study. If a subject withdraws from the study with an existing adverse event, regardless of the relationship to the study device or procedure, the subject will only be followed for a maximum of 104 days following their study procedure date.

Table 2: DAWN Study Time and Clinical Assessment Schedule

Event	Screening/ Baseline	Procedure (Treatment Arm Only)	24 Hr (-6/+24) (post randomizatio n)	Day 5-7 / Discharge (whichever is earlier)	Discharg e	Day 30 ± 14	Day 90 ± 14
Inclusion/Exclusion Criteria	✓						
Demographics/Medical History/Baseline Medications	✓						
Baseline Characteristics	✓						
Baseline Labs	✓						
Informed Consent	✓						
Randomization (t=0)	✓						
Angiography Procedure Details (Treatment Arm only)		✓					
mRS [†]	✓ (pre stroke)			✓ [†]		✓ [†]	✓ [†]
NIHSS	✓ *		✓ **	✓		✓	✓
Neuro imaging (to assess for hemorrhage, occlusion location/vessel patency & infarct volume)***	✓ MR-DWI/MRA or CT/CTA/CTP		✓ MR-DWI/MRA or CT/CTA	✓ MR-DWI or CT (optional)			
AEs/SAEs (from time of randomization)		✓	✓	✓		✓	✓
Concomitant Medications		✓	✓	✓		✓	✓
In Hospital Med Management					✓		
Intubation Details					✓		
UB04					✓		

*NIHSS should be obtained within 1 hour of corresponding core infarct measurement.

** NIHSS should be obtained within 2 hours of the 24 (-6/+24) hour neuro-imaging to determine presence/absence of hemorrhage. [†] Must be conducted by an individual blinded to the treatment arm.

*** CT/MR and Angiographic images should be de-identified before being submitted to Stryker NV or core lab.

4.9. Analyses Schedule

Data analyses will occur according to the required timeframes for submission of study reports to the Food and Drug Administration (FDA). A final analysis will occur upon study completion.

4.10. 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 of Study protocol.

4.10.1. 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.

4.10.2. 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 RAPID 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.

4.10.3 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 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.

4.10.4. 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.

4.11. Efficacy Analyses

The final analysis 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:

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

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 team using SAS, version 9.2 or higher.

4.11.1. Subject Accountability

Subject disposition will be summarized for all randomized Subjects. The number and percentage of Subjects in the following categories will be presented by treatment arm and overall:

- Subjects randomized;
- Subjects randomized and not treated;
- Subjects treated;
- Subjects with 24 hour follow-up visit, Day 5-7/Discharge, Day30, and Day 90;
- Subjects completed the study;
- Subjects discontinued from the study.

Treatment arms will be compared for the incidence and reason for study termination using counts and percentages. A summary of Subject status at the end of the study period, i.e., completed follow-up (to study end date or death) or lost to follow-up (LFU) will also be generated.

4.11.2. Demographics and Baseline Characteristics

Baseline data will be analyzed to assess the comparability of treatment arms. Subject demographics, clinical characteristics, key elements of past medical history, medications, pre-

treatment NIHSS and Modified Rankin Scores and baseline characteristics will be summarized using descriptive statistics. Differences and risk ratios (as appropriate) between treatment arms and their 95% confidence intervals will be calculated for variables collected.

Statistical testing for differences between treatment arms will be performed by t-test assuming un-equal variances for continuous variables and Chi-squared/ Fisher's Exact test for categorical data. Unless otherwise stated, comparisons made between two arms will be performed using 2-sided tests at an $\alpha=0.05$ significance level.

Only ITT population will be employed for these data analyses.

- Age, defined as the number of years from date of birth to date of randomization (continuous)
- Gender (male, female)
- Race/ethnic origin (Caucasian, African American, Asian, Indian, Native American Indian/Alaska native, Native Hawaiian/Pacific Islander, Other)
- BMI

The incidence of pre-specified events[wake-up stroke, witnessed/un-witnessed stroke, etc.], conditions [hypertension, Heart Failure, Coronary Artery Disease, Extracranial Carotid Artery Disease, Peripheral Vascular Disease, Diabetes Mellitus, Dyslipidemia, Smoke history, Previous Transient Ischemic Attack, Previous Ischemic Stroke, Previous Intra-cerebral Hemorrhage, Previous History of known ICAD] will be summarized in each treatment arm using counts and percentages.

4.11.3. Clinical Evaluation

National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), and Neuro imaging assessments will be summarized by counts and percentages for two treatment arms at Baseline, 24 Hr(-6/+24), Day5-7/Discharge, 30 days (± 14 days), and 90 days (± 14 days) post-procedure, if applicable.

4.11.4. Study Device Accountability

For the study device accountability, the number of study devices used, the number of subjects with study devices used, will be calculated and summarized.

4.11.5. Analysis of Primary Effectiveness Endpoints

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.

4.11.6. Analysis of Secondary Effectiveness Endpoints.

The analysis population to prove the efficacy of the Trevo® Retriever consists of two arms: Treatment arm and Control arm. The two arms are defined as below.

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 17 of 24

- a. Treatment arm: the subjects who is randomized to the Trevo thrombectomy plus medical management.
- b. Control arm: the subjects who is randomized to the medical management alone.

The following Secondary Effectiveness Endpoints will be analyzed:

Both Arms:

- Proportion of subjects with a good functional outcome at 90 days, defined as mRS 0-2 will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- 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 will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- Difference in all-cause mortality rates between the two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- Difference in median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if contraindicated for MR) will be presented with n, mean, median, interquartile, standard deviation, minimum, and maximum between two treatment arms. P-values will be calculated with t-test assuming un-equal variances to compare the difference between two treatment arms.
- Difference in revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA between the two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

Treatment Arm Only:

Analysis of vessel reperfusion rates, by angiography measurement of modified TICI $\geq 2b$ will be consistently reported with the count, rate and exact Clopper-Pearson 95% CI separately by post device and post procedure in treatment arm.

The enriched populations will be employed for secondary effectiveness endpoints analysis (refer to adaptive design plan in Appendix F of study protocol).

4.11.7. Pooling Across Sites

Results for the primary efficacy endpoint will be presented by sites and treatment arms. Poolability across sites will be assessed using Proc GLM in SAS to fit an ANCOVA model on the weighted mRS with terms for treatment arm, site, and the interaction of treatment arm 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 Proc Mixed in SAS using a hierarchical model with random site effect. Sites with fewer than 10 Subjects will be combined and treated as one site in examining the pooling.

4.11.8. Other Pre-planned Analyses

Both Arms:

Incidence of symptomatic ICH (per the SITS MOST definition) will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

Treatment Arm only:

Summary of functional independence (mRS 0-2) by reperfusion status, will be provided by N, percentage and exact Clopper-Pearson 95% CI, separately by post-device and post-procedure in treatment arm.

4.11.9. Health Economic Evaluation

The health economic evaluation will not be part of this SAP. However, the analyses to compare overall health care costs and resource utilization between mechanical intervention and standard medical care may be needed in the future.

4.12. Safety analysis

4.12.1 Adverse Events

Adverse Event Definitions and Classification

Term	Definition	Reference
------	------------	-----------

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)	<p>Any untoward and unintended response to a medical device.</p> <p><i>Note 1:</i> This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.</p> <p><i>Note 2:</i> This definition includes any event that is a result of a user error.</p>	ISO 14155-1
Serious adverse event (SAE)	<p>An adverse event that:</p> <ul style="list-style-type: none"> • 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 in Subject 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.

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

Unknown – There is not enough information to make a determination.

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.

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

Unknown – There is not enough information to make a determination.

4.12.2. Summaries of Adverse Events

All summaries of adverse events will be based on events that occurred during the study. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of subjects experiencing adverse events will be summarized by system organ class and preferred term. Summaries by relationship to the study device and procedure will also be provided. Serious adverse events will be summarized separately.

Results will be presented for each of the following 3 groups

- Subjects randomized to the Treatment arm,
- Subjects randomized to the Control arm, and
- All randomized subjects.

4.12.3. Analysis of Primary Safety Endpoints

Both Arms:

Incidence of stroke-related mortality at 90 days will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 21 of 24

ITT population will be used for the analysis of Primary Safety Outcome.

4.12.4. Analysis of Secondary Safety Outcome

Both Arms:

- a. Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero) will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- b. 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, which will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

Treatment Arm:

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

The number of Subjects with SAEs will be summarized by CEC adjudicated category described as above, separately by specified categorization, i.e. procedure-related vs. device-related. N, percentage and exact Clopper-Pearson 95% CI of the variables will be provided in each category.

5. PROGRAMMING CONSIDERATIONS

5.1. Statistical Software

All statistical analyses will be done using The SAS System software, version 9.2 or higher. (Copyright © 2002-2014 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

Concentric Medical, a business unit of Stryker Neurovascular
DAWN Trial Statistical Analysis Plan
CDM10000704, Ver. AA
Page 22 of 24

5.2. Methods for handling missing data especially the AE start date

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measures. The distribution of prognostic factors between Subjects with and without data will be examined. This is used as a preliminary approach to assess whether or not missing data occurs randomly. Imputation for missing data is deemed necessary if missing data is associated with key prognostic factors and >20% of values of that variable are missing. Sensitivity analyses will be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be examined for their validity; all data will be included. Any value judged to be invalid will be queried.

For the purposes of determining time to Adverse Event, missing and partial dates will be handled as follows. If the entire adverse event start date is missing then the procedure date will be used for the start date. If the month and the day of the month are missing but the year is available and the year is the same as the year of the procedure then the procedure date will be used for the start date. If the year is greater than the year of the procedure then January 1st will be used for the month and day of the start date. If the day is missing, but the month and year are available, then the 1st day of the month will be used as the day of the start date unless the imputed date would occur before the procedure in which case the procedure date will be used for the start date of the adverse event.

Note: With the exception of following special cases, this conservative scheme ensures that an AE with a partially or completely missing start-date will be treated as post-procedural.

Special Cases on Missing AE Start-dates

Using the above rules for the handling of missing AE start-dates, if the assumed AE start-date:

- is later than the reported AE stop-date, the assumed AE start-date will be reset and assumed to be the AE stop-date.
- If, based on the above rules, it cannot be determined whether the AE was taken prior to the study procedure, it will be assumed to be post-procedural.

5.3. Rules for calculating rates and handling denominators

For Safety events, binary rates will be calculated using as a denominator as the number of all Subjects in the study, regardless of their follow-up time.

Other binary rates such as mRS or NIHSS will be calculated using a denominator as the total number of the available data for the outcome, excluding missing values.

6. STATISTICAL REPORT TEMPLATE

The report template will be established prior to database lock.

7. REFERENCES

- Fleiss, J.L. (1981). *Statistical Methods for Rates and Proportions*, Wiley, New York.
- Piantadosi, S. (2005) *Clinical Trials: A Methodologic Perspective*, Wiley, New York.
- SAS Institute Inc., *SAS[®] Version 9.4 software*, Cary, NC.

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Statistical Analysis Plan

DAWN Trial

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

Updated Date: 05/11/2017

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Concentric Medical, a business unit of Stryker Neurovascular
Fremont, CA USA

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

TABLE of CONTENTS

1.	OVERVIEW STATISTICAL PLAN	6
2.	STUDY OBJECTIVES.....	6
2.1.	Primary Objective	6
2.2.	Secondary Objectives	6
3.	STUDY DESIGN.....	7
3.1.	Study Endpoints	7
3.1.1.	<i>Primary Endpoint</i>	7
3.1.2.	<i>Secondary Endpoints</i>	8
3.1.3.	<i>Primary Safety Outcome</i>	8
3.1.4.	<i>Secondary Safety Outcome</i>	8
3.2.	Randomization	9
4.	STATISTICAL METHODS	10
4.1.	Primary Statistical Null Hypothesis	10
4.2.	Study Success	10
4.3.	The Secondary Efficacy and Safety Endpoints	11
4.4.	Comparability Analyses of the Patient Populations	12
4.5.	Subgroup Analysis.....	12
4.6.	Sample Size Estimate and Justification	12
TABLE 1.	DISTRIBUTION OF MRS OUTCOMES FOR THE CONTROL ARM IN THE SIMULATIONS	13
4.7.	Control of Systematic Error/Bias.....	13
4.8.	Eligibility of Subjects, Exclusions, and Missing Data.....	14
4.9.	Population Definitions	14
4.10.	Analysis Populations.....	15
4.11.	Estimated Duration of Subject Participation	16
TABLE 2.	DAWN STUDY TIME AND CLINICAL ASSESSMENT SCHEDULE	17
4.12.	Analyses Schedule.....	17
4.13.	Interim Analysis	18
4.13.1.	<i>Interim Monitoring for Early Futility</i>	18
4.13.2.	<i>Enrichment</i>	19
4.13.3.	<i>Interim Monitoring for Expected Success</i>	20

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

4.13.4. <i>Longitudinal Model</i>	20
4.14. <i>Efficacy Analyses</i>	20
4.15. <i>Subject Accountability</i>	21
4.15.1. <i>Demographics and Baseline Characteristics</i>	22
4.15.2. <i>Clinical Evaluation</i>	23
4.15.3. <i>Study Device Accountability</i>	23
4.15.4. <i>Analysis of Primary Effectiveness Endpoints</i>	23
4.15.5. <i>Analysis of Secondary Effectiveness Endpoints</i>	23
4.15.6. <i>Pooling Across Sites</i>	25
4.15.7. <i>Other Pre-planned Analyses</i>	25
4.15.8. <i>Health Economic Evaluation</i>	26
5. SAFETY ANALYSIS	27
5.1. <i>Adverse Events</i>	27
TABLE 3. <i>ADVERSE EVENT DEFINITIONS AND CLASSIFICATION</i>	27
5.2. <i>Summaries of Adverse Events</i>	28
5.3. <i>Analysis of Primary Safety Endpoints</i>	29
5.4. <i>Analysis of Secondary Safety Outcome</i>	29
6. PROGRAMMING CONSIDERATIONS	30
6.1. <i>Statistical Software</i>	30
6.2. <i>Methods for Handling Missing Data Especially the AE Start Date</i>	31
6.3. <i>Rules for Calculating Rates and Handling Denominators</i>	31
7. STATISTICAL REPORT TEMPLATE	32
8. REFERENCES	32
9. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	32
TABLE 4. <i>ADVERSE EVENT DEFINITIONS AND CLASSIFICATION</i>	32

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Original	Revision	Justification
Version AA established 04Jun2014	See changes below.	Plan was established a-priori. Changed in 2017 to align with version AD of protocol per FDA request.
List of abbreviations was at beginning of report	Moved list of abbreviations to the end of the document	Author preference
The primary endpoint is a comparison of the difference between the average weighted modified Rankin Scale score at 90 days post randomization between the two arms. 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. of Protocol.	<p>The primary endpoint is the 90-day clinical outcomes assessed by the modified Rankin scale (mRS).</p> <p>There will be two, hierarchically nested, co-primary analyses of this endpoint. The first primary endpoint analysis will consist of 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 this analysis, 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. If this primary endpoint analysis is positive, the hierarchically nested second co-primary endpoint analysis will be conducted, and will be 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).</p>	The nested co-primary endpoint was added for use when the study is considered in the regulatory setting. It will be used by FDA, which requested this additional criterion for regulatory consideration.
	Updated document style, headers, and footers to SNV standards	

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

1. OVERVIEW STATISTICAL PLAN

This document contains a detailed description of the Statistical Analysis Plan (SAP) for the data from the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention (DAWN).

It provides specifications for the statistical analyses of the data to be prepared and presented for the purpose of demonstrating efficacy and safety to fulfill Food and Drug Administration (FDA) IDE requirements.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA. This plan may be revised during the study to accommodate any study plan change request by FDA, to make changes to adapt to unexpected issues in study execution or data that affects planned analyses. The final plan will be issued prior to final data lock. Furthermore, as no analysis plan prepared in advance of the data can be definitive, the final report may contain additional tables, footnotes or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final report.

2. STUDY OBJECTIVES

2.1. 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.

2.2. 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

3. STUDY DESIGN

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.

Up to a total of 50 worldwide sites with <= 20 sites outside of the U.S will participate in the study. A maximum of 500 subjects are planned to be enrolled; 250 in the Treatment arm and 250 in the Control arm over an approximate 36-month recruitment period. Total study duration will be approximately 39 months (+/- 9 months), including one 24 (-6/+24) hours' MRI/MRA or CT/CTA and NIHSS assessment followed by Day 5-7, 30 (\pm 14), and Day 90 (\pm 14) clinical assessments.

3.1. Study Endpoints

3.1.1. Primary Endpoint

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

There will be two, hierarchically nested, co-primary analyses of the primary outcome.

1. The first primary analysis will be a test of superiority for the active versus the control using a weighted utility value for each mRS score at 90-days. 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]
2. If the first primary endpoint analysis is positive, the hierarchically nested second co-primary endpoint analysis will be conducted, and will be a test of superiority for the active versus the control comparing the proportion of functional independence (mRS 0-2) at 90 days post randomization.

Findings with this approach will be interpreted in the following manner:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

- 1) The utiliy-weighted mRS analysis is neutral - the study will be considered to have a neutral result.
- 2) The utiliy-weighted mRS analysis is positive, and the nested dichotomous analysis is neutral - the study will be considered to have demonstrated benefit in reducing (shifting) disability but not benefit in increasing functional independence.
- 3) The utiliy-weighted mRS analysis is positive, and the nested dichotomous analysis is neutral If the dichotomous mRS is also positive - the study will be considered to have demonstrated benefit in reducing (shifting) disability and also benefit in increasing functional independence.

3.1.2. Secondary Endpoints

Both Arms:

1. 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
2. Proportion of subjects suffering all-cause mortality between the two groups.
3. Difference in median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if contraindicated for MR)
4. Proportion of revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA.

Treatment Arm Only:

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

3.1.3. Primary Safety Outcome

Both Arms:

1. Incidence of stroke-related mortality at 90 days

3.1.4. Secondary Safety Outcome

Both Arms:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

- a. Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero)
- b. 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:

- c. 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

3.2. Randomization

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). Blocks will be assigned to all sites including the stratification mapping to maintain balance at all sites.

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. In case of any protocol violations all efficacy analyses will be based on an intent-to-treat analysis where subjects are classified by the group in which they are randomized.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

4. STATISTICAL METHODS

4.1. Primary Statistical Null Hypothesis

There are hierarchically nested co-primary analyses of the 90-day mRS values between the two arms. For the analysis of the weighted mRS values at 90-days the null hypothesis is that the mean weighted mRS value is equal in the two treatment groups. The alternative hypothesis to be tested is that the mean utility is greater in the Trevo Thrombectomy plus Medical Management (Active) treatment arm than the Medical Management alone (Control). For the analysis of the proportion of subjects functionally independent (mRS 0-2) at 90 days in the null hypothesis is that the probability of a functionally independent subject in each treatment group are equal, with an alternative that the probability of a functionally independent subject on the Active arm is larger than for the control arm.

For each co-primary hypothesis test the analysis is based on a Bayesian analysis. Success will be considered for the weighted mRS co-primary analysis first, and will be declared if the posterior probability of the alternative hypothesis (superiority) is sufficiently large. Only if the weighted mRS co-primary analysis is positive will analysis then proceed to the nested dichotomous analysis. For the nested analysis, success will be declared if the posterior probability of the alternative hypothesis (superiority) is sufficiently large. The threshold for success if no adaptive enrichments are made is 0.986, and this threshold increases if adaptive enrichments occur. The adjusted thresholds are to control type I error and are detailed in the Adaptive Design Plan in Appendix F of Study Protocol.

4.2. Study Success

If the utility-weighted mRS analysis is positive, the study will be considered to have had success in demonstrating benefit in reducing (shifting) disability.

If the utility-weighted mRS analysis is neutral, no further analysis for study success will be performed.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

If the utility-weighted mRS analysis is positive, and the nested dichotomous analysis is neutral - the study will be considered to have had success in demonstrating benefit in reducing (shifting) disability but not benefit in increasing functional independence.

If the utiliy-weighted mRS analysis is positive, and the nested dichotomous analysis is also positive - the study will be considered to have had success in demonstrating benefit in reducing (shifting) disability and also success in demonstrating benefit in increasing functional independence.

4.3. The Secondary Efficacy and Safety Endpoints

For binary outcomes, the count and percentage will be provided for each treatment arm. The difference in the rate between the treatment arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test as appropriate. Fisher's exact test is used in place of the Chi-square test when at least one cell count in the 2x2 table has expected value less than 5 or total sample size is less than or equal to 40. The p-value will be denoted with an asterisk (*) in the case where a Fisher's exact test was used.

Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

$$SE = \sqrt{(1-p_1)/n_{11} + (1-p_2)/n_{21}}.$$

$$95\% \text{ CI} = RR \cdot \exp(\pm 1.96 \cdot SE).$$

For continuous outcomes, n, mean, median, interquartile (Q3-Q1), standard deviation, minimum, and maximum values will be provided for each treatment arm. P-values will be calculated using a t-test assuming un-equal variances to compare the difference between two treatment arms.

Difference = Trevo thrombectomy plus medical management – medical management.

$$95\% \text{ CI} = \text{Diff} \pm 1.96 \cdot SE$$

$$SE = \sqrt{(p_1 q_1/n_1 + p_2 q_2/n_2)} \text{ for proportions,}$$

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

$SE = \sqrt{[(1/n_1 + 1/n_2)\{(n_1-1)s_{12}^2 + (n_2-1)s_{22}^2\}/(N-2)]}$ for continuous variables.

For ordinal variables a Wilcoxon rank sum test will be used and footnoted.

4.4. Comparability Analyses of the Patient Populations

These analyses are intended to determine the similarity of treatment groups and study sites with respect to important demographic or other variables, either known or suspected to have an influence on the outcome variables. The absence of similarity for any baseline variable will identify that variable as a potential covariate in subsequent safety and effectiveness multivariable analyses. The data for each baseline variable will be presented descriptively. For quantitative variables like age, the mean, standard deviation (SD), median, minimum, and maximum will be presented. For qualitative variables like gender, the number with the characteristic, the total number evaluated, the rate, and the exact 95% binomial confidence limits will be presented.

4.5. Subgroup Analysis

Pre-specified subgroups were developed a priori for scientific interest and exploratory analyses. Multivariate and subgroup analyses are considered supportive without control of alpha and the additional endpoint analyses are likewise supportive without control of alpha.

The following pre-specified subgroups will be evaluated:

- Age (< 80 vs ≥ 80)
- Sex
- Admission NIHSS (median split)
- TLSW between 6 and ≤ 12 hours vs >12 to 24 hours
- Clinical imaging mismatch (CIM) category
- Wake-Up, Witnessed, and Unwitnessed
- Baseline occlusion location (ICA vs. M1)

4.6. Sample Size Estimate and Justification

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

We investigated treatment effects that increased the expected weight in the active arm 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 this trial is not powered (30%) for this 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 significant 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); MR RESCUE penumbral pattern with IV tPA arm (N=34); PROACT II heparin arm (N=59); MELT no treatment arm (N=57); DEFUSE 2 Target Mismatch without reperfusion arm (N=32); Merci Registry non-revascularized, non-intubated, treated \geq 6 hours (N=30) [Sponsor-derived from raw dataset]; Natural History of MCA and ICA occlusions (N=40); and SENTIS no treatment arm (N=106). The distribution of the mRS outcomes for the control arm used in the simulations is shown in **Table 1**.

TABLE 1. 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

4.7. 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

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.

4.8. 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 the 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 a multiple imputation model. In case of missing 90-day and missing 30-day mRS values, multiple imputation models will incorporate the day 5-7mRS; if that also missing, the subject will be counted as a failure (mRS 6). For conventional statistical analysis of the 90 day mRS and descriptive statistics (e.g. distribution of mRS) will use LOCF of 30 day data. Refer to the adaptive design plan for details in Appendix F of study protocol.

4.9. 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).

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Enrolled: Includes any subject who has been randomized based upon the results of the RAPID 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.

4.10. Analysis Populations

Intent-to-Treat (ITT): Includes all enrolled/randomized subjects. All randomized subjects will be included in the ITT analysis, where the arm classification is based on the randomized arm, even if they never receive it or receive treatment with another procedure. If the final analysis is only on the enriched population (refer to adaptive design plan in Appendix F of study protocol) then only those subjects in the enriched group will be included in the final analysis, based in ITT. This population is the primary population for all efficacy parameters.

As-Treated Analysis (AT): 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

4.11. Estimated Duration of Subject Participation

Subjects will be followed for 90 (\pm 14) days post-procedure, with data collection 24(-6/+24) hours post randomization, on the day of hospital discharge or 5 to 7 days (whichever occurred sooner), 30 days (\pm 14 days), and 90 days (\pm 14 days) post-procedure. Subjects who do not withdraw prematurely from the study will be followed for a maximum of 104 days following the study procedure. Any subject who discontinues from the study for any reason will be followed to monitor safety for the duration of the study. If a subject withdraws from the study with an existing adverse event, regardless of the relationship to the study device or procedure, the subject will only be followed for a maximum of 104 days following their study procedure date.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

TABLE 2. DAWN STUDY TIME AND CLINICAL ASSESSMENT 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 (t=0)	✓						
Angiography Procedure Details (Treatment Arm only)		✓					
mRS [†] (pre stroke)	✓			✓ [†]		✓ [†]	✓ [†]
NIHSS	✓ *		✓ **	✓		✓	✓
Neuro imaging (to assess for hemorrhage, occlusion location/vessel patency & infarct volume)***	✓	MR-DWI/MRA or CT/CTA/CTP	✓	✓	MR-DWI or CT (optional)		
AEs/SAEs (from time of randomization)		✓	✓	✓		✓	✓
Concomitant Medications		✓	✓	✓		✓	✓
In Hospital Med Management					✓		
Intubation Details					✓		
UB04					✓		

*NIHSS should be obtained within 1 hour of corresponding core infarct measurement.

** NIHSS should be obtained within 2 hours of the 24 (-6/+24) hour neuro-imaging to determine presence/absence of hemorrhage. [†] Must be conducted by an individual blinded to the treatment arm.

*** CT/MR and Angiographic images should be de-identified before being submitted to Stryker NV or core lab.

4.12. Analyses Schedule

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Data analyses will occur according to the required timeframes for submission of study reports to the Food and Drug Administration (FDA). A final analysis will occur upon study completion.

4.13. 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 adaptations that may be made at the interims are to:

- Stop the trial 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.

The rules for each decision/adaptation are defined below. Additional details pertaining to statistical models are given in the adaptive design plan in Appendix F of Study protocol.

4.13.1. *Interim Monitoring for Early Futility*

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

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.

4.13.2. 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 RAPID 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) cc infarct sizes has less than 40% posterior probability of an average positive treatment effect on mRS, 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.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

4.13.3. 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 or no enrichment has been made and at least 200 total subjects have been randomized. 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.

In order that the trial stop for expected success, the predictive probability of trial success must exceed the threshold described above, and the analogous predictive probability of trial success for the dichotomized version of the utility function must also exceed the same threshold. The dichotomized utility function is also discussed in Appendix F.

4.13.4. 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 multiply imputing final mRS outcomes for subjects with known 30-day mRS but unknown 90-day mRS.

4.14. Efficacy Analyses

The final analysis will be performed only on the enriched population if an enrichment occurs, and assumes a constant treatment effect over all infarct sizes that are in the population at the end of the trial.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

The trial is considered successful if there is sufficiently high posterior probability that the treatment effect is positive. The threshold for success is adjusted (increased) to account for any enrichment that occurred to 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:

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

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 team using SAS, version 9.4 or higher.

4.15. Subject Accountability

Subject disposition will be summarized for all randomized Subjects. The number and percentage of Subjects in the following categories will be presented by treatment arm and overall:

- Subjects randomized;
- Subjects randomized and not treated;
- Subjects treated;
- Subjects with 24 hour follow-up visit, Day 5-7/Discharge, Day30, and Day 90;
- Subjects completed the study;
- Subjects discontinued from the study.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Treatment arms will be compared for the incidence and reason for study termination using counts and percentages. A summary of Subject status at the end of the study period, i.e., completed follow-up (to study end date or death) or lost to follow-up (LFU) will also be generated.

4.15.1. Demographics and Baseline Characteristics

Baseline data will be analyzed to assess the comparability of treatment arms. Subject demographics, clinical characteristics, key elements of past medical history, medications, pre-treatment NIHSS and Modified Rankin Scores and baseline characteristics will be summarized using descriptive statistics. Differences and risk ratios (as appropriate) between treatment arms and their 95% confidence intervals will be calculated for variables collected.

Statistical testing for differences between treatment arms will be performed by t-test assuming un-equal variances for continuous variables and Chi-squared/ Fisher's Exact test for categorical data. Unless otherwise stated, comparisons made between two arms will be performed using 2-sided tests at an $\alpha=0.05$ significance level.

Only ITT population will be employed for these data analyses.

- Age, defined as the number of years from date of birth to date of randomization (continuous)
- Gender (male, female)
- Race/ethnic origin (Caucasian, African American, Asian, Indian, Native American Indian/Alaska native, Native Hawaiian/Pacific Islander, Other)
- BMI

The incidence of pre-specified events[wake-up stroke, witnessed/un-witnessed stroke, etc.], conditions [hypertension, Heart Failure, Coronary Artery Disease, Extracranial Carotid Artery Disease, Peripheral Vascular Disease, Diabetes Mellitus, Dyslipidemia, Smoke history,

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Previous Transient Ischemic Attack, Previous Ischemic Stroke, Previous Intra-cerebral Hemorrhage, Previous History of known ICAD] will be summarized in each treatment arm using counts and percentages.

4.15.2.Clinical Evaluation

National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), and Neuro imaging assessments will be summarized by counts and percentages for two treatment arms at Baseline, 24 Hr(-6/+24), Day5-7/Discharge, 30 days (± 14 days), and 90 days (± 14 days) post-procedure, if applicable.

4.15.3.Study Device Accountability

For the study device accountability, the number of study devices used, the number of subjects with study devices used, will be calculated and summarized.

4.15.4.Analysis of Primary Effectiveness Endpoints

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.

4.15.5.Analysis of Secondary Effectiveness Endpoints

The analysis population to prove the efficacy of the Trevo® Retriever consists of two arms: Treatment arm and Control arm. The two arms are defined as below.

- a. Treatment arm: the subjects who are randomized to the Trevo thrombectomy plus medical management.
- b. Control arm: the subjects who are randomized to the medical management alone.

The following Secondary Effectiveness Endpoints will be analyzed:

Both Arms:

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

- 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 will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher’s exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- Difference in all-cause mortality rates between the two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher’s exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- Difference in median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if contraindicated for MR) will be presented with n, mean, median, interquartile, standard deviation, minimum, and maximum between two treatment arms. P-values will be calculated with t-test assuming un-equal variances to compare the difference between two treatment arms.
- Difference in revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA between the two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher’s exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Treatment Arm Only:

Analysis of vessel reperfusion rates, by angiography measurement of modified TICI > 2b will be consistently reported with the count, rate and exact Clopper-Pearson 95% CI separately by post device and post procedure in treatment arm.

The enriched populations will be employed for secondary effectiveness endpoints analysis (refer to adaptive design plan in Appendix F of study protocol).

4.15.6. Pooling Across Sites

Results for the primary efficacy endpoint will be presented by sites and treatment arms. Poolability across sites will be assessed using Proc GLM in SAS to fit an ANCOVA model on the weighted mRS with terms for treatment arm, site, and the interaction of treatment arm 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 Proc Mixed in SAS using a hierarchical model with random site effect. Sites with fewer than 10 Subjects will be combined and treated as one site in examining the pooling.

4.15.7. Other Pre-planned Analyses

Both Arms:

Incidence of symptomatic ICH (per the SITS MOST definition) will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

Treatment Arm only:

Summary of functional independence (mRS 0-2) by reperfusion status, will be provided by N, percentage and exact Clopper-Pearson 95% CI, separately by post-device and post-procedure in treatment arm.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

4.15.8. Health Economic Evaluation

The health economic evaluation will not be part of this SAP. However, the analyses to compare overall health care costs and resource utilization between mechanical intervention and standard medical care may be needed in the future.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

5. SAFETY ANALYSIS

5.1. Adverse Events

TABLE 3. 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. <i>Note 1:</i> This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. <i>Note 2:</i> This definition includes any event that is a result of a user error.	ISO 14155-1
Serious adverse event (SAE)	An adverse event that: <ul style="list-style-type: none">• 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 in Subject 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

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.

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

Unknown – There is not enough information to make a determination.

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.

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

Unknown – There is not enough information to make a determination.

5.2. Summaries of Adverse Events

All summaries of adverse events will be based on events that occurred during the study. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

of subjects experiencing adverse events will be summarized by system organ class and preferred term. Summaries by relationship to the study device and procedure will also be provided. Serious adverse events will be summarized separately.

Results will be presented for each of the following 3 groups

- Subjects randomized to the Treatment arm,
- Subjects randomized to the Control arm, and
- All randomized subjects.

5.3. Analysis of Primary Safety Endpoints

Both Arms:

Incidence of stroke-related mortality at 90 days will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

ITT population will be used for the analysis of Primary Safety Outcome.

5.4. Analysis of Secondary Safety Outcome

Both Arms:

- a. Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero) will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.
- b. 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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

score, which will be presented by providing the count and percentage for each treatment arm. The difference in the percentage between two arms and the 95% CI for the difference will be calculated using the normal approximation to binomial. P-values will be calculated by the Chi-squared test or Fisher's exact test as appropriate. Relative Risk (RR) was provided as Trevo thrombectomy plus medical management / medical management.

Treatment Arm:

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

The number of Subjects with SAEs will be summarized by CEC adjudicated category described as above, separately by specified categorization, i.e. procedure-related vs. device-related. N, percentage and exact Clopper-Pearson 95% CI of the variables will be provided in each category.

6. PROGRAMMING CONSIDERATIONS

6.1. Statistical Software

All statistical analyses will be done using The SAS System software, version 9.4 or higher.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

6.2. Methods for Handling Missing Data Especially the AE Start Date

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measures. The distribution of prognostic factors between Subjects with and without data will be examined. This is used as a preliminary approach to assess whether or not missing data occurs randomly. Imputation for missing data is deemed necessary if missing data is associated with key prognostic factors and >20% of values of that variable are missing. Sensitivity analyses will be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be examined for their validity; all data will be included. Any value judged to be invalid will be queried.

For the purposes of determining time to Adverse Event, missing and partial dates will be handled as follows. If the entire adverse event start date is missing then the procedure date will be used for the start date. If the month and the day of the month are missing but the year is available and the year is the same as the year of the procedure then the procedure date will be used for the start date. If the year is greater than the year of the procedure then January 1st will be used for the month and day of the start date. If the day is missing, but the month and year are available, then the 1st day of the month will be used as the day of the start date unless the imputed date would occur before the procedure in which case the procedure date will be used for the start date of the adverse event.

Note: With the exception of following special cases, this conservative scheme ensures that an AE with a partially or completely missing start-date will be treated as post-procedural.

Special Cases on Missing AE Start-dates

Using the above rules for the handling of missing AE start-dates, if the assumed AE start-date:

- is later than the reported AE stop-date, the assumed AE start-date will be reset and assumed to be the AE stop-date.
- If, based on the above rules, it cannot be determined whether the AE was taken prior to the study procedure, it will be assumed to be post-procedural.

6.3. Rules for Calculating Rates and Handling Denominators

For Safety events, binary rates will be calculated using as a denominator as the number of all Subjects in the study, regardless of their follow-up time.

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Other binary rates such as mRS or NIHSS will be calculated using a denominator as the total number of the available data for the outcome, excluding missing values.

7. STATISTICAL REPORT TEMPLATE

The report template will be established prior to database lock.

8. REFERENCES

Fleiss, J.L. (1981). Statistical Methods for Rates and Proportions, Wiley, New York.

Piantadosi, S. (2005) Clinical Trials: A Methodologic Perspective, Wiley, New York.

SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.

9. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

TABLE 4. ADVERSE EVENT DEFINITIONS AND CLASSIFICATION

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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Abbreviation	Full Term
CT	Computerized Tomography
CTA	Computerized Tomography Angiography
CTP	Computerized Tomography Perfusion
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
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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Abbreviation	Full Term
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
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
SBP	Systolic Blood Pressure
SICH	Symptomatic Intracranial Hemorrhage
TICI	Thrombolysis in Cerebral Infarction
TIMI	Thrombolysis in Myocardial Infarction

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

Stryker Neurovascular

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Abbreviation	Full Term
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

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION

DAWN STATISTICAL ANALYSIS PLAN SUMMARY OF CHANGES

Document Title: DAWN™ Trial Statistical Analysis Plan

Document Number: CDM10000704

Rev: AB

Original	Revision	Justification
Version AA established 04Jun2014	See changes below.	Plan was established a-priori. Changed in 2017 to align with version AD of protocol per FDA request.
List of abbreviations was at beginning of report	Moved list of abbreviations to the end of the document	Author preference
The primary endpoint is a comparison of the difference between the average weighted modified Rankin Scale score at 90 days post randomization between the two arms. 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. of Protocol.	<p>The primary endpoint is the 90-day clinical outcomes assessed by the modified Rankin scale (mRS).</p> <p>There will be two, hierarchically nested, co-primary analyses of this endpoint. The first primary endpoint analysis will consist of 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 this analysis, 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. If this primary endpoint analysis is positive, the hierarchically nested second co-primary endpoint analysis will be conducted, and will be 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).</p>	The nested co-primary endpoint was added for use when the study is considered in the regulatory setting. It will be used by FDA, which requested this additional criterion for regulatory consideration.
	Updated document style, headers, and footers to SNV standards	

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION