

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

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Stryker Neurovascular

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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	

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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.

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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 (± 14), and Day 90 (± 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:

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- 1) The utility-weighted mRS analysis is neutral - the study will be considered to have a neutral result.
- 2) The utility-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 utility-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 TIC1 $\geq 2b$.

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:

- 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.

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.

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 utility-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.

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

$$SE = \sqrt{p_1q_1/n_1 + p_2q_2/n_2} \text{ for proportions,}$$

$SE = \sqrt{[(1/n_1 + 1/n_2)\{(n_1-1)s_1^2 + (n_2-1)s_2^2\}/(N-2)]}$ 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:

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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 ≥ 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.

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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 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).

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.

4.11. 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 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.

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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/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.

4.12. Analyses Schedule

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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.

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.

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.

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.

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,

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:

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- 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.

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Treatment Arm Only:

Analysis of vessel reperfusion rates, by angiography measurement of modified TIC1 > 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.

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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.

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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

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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

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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

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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.

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.

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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

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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

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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

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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

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