ASSIST™ Registry Protocol

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Stryker Neurovascular

Document Title: ASSIST™ Registry Protocol

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Study Centers	A current list of sites will be maintained in the Sponsor's study files
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ASSIST™ Registry Protocol Signature Page

Study Title: ASSIST™ Registry

Study Center: _____

(Print name of study center)

We, the undersigned, have read and understand the protocol specified above and agree on its content. We agree to perform and conduct the study as described in the protocol. In addition, when applicable, we agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

_____

Principal Investigator Signature

_____ _____

Printed Name DD / MMM / YYYY

_____

Co-Investigator Signature ☐ N/A

_____ _____

Printed Name DD / MMM / YYYY

Clinical Protocol Synopsis	
Primary Objective	The purpose of this Registry is to assess the procedural success and clinical outcomes associated with various operator techniques for mechanical thrombectomy in large vessel occlusions (LVO) in the anterior circulation. This Registry will also collect data, including time-to-treatment and quality of life measures, to allow for subset analyses that may be used for regulatory submissions and/or reimbursement dossiers.
Primary Clinical Outcome	1. Severity of disability at Day 90 (± 14) assessed by modified Rankin Scale (mRS) with a good functional outcome defined as mRS of 0-2 for each technique
Secondary Clinical Outcomes	1. Excellent functional outcome defined as mRS of 0-1 at Day 90 (± 14) 2. An "early response" at Discharge/Day5-7 (whichever is earlier) defined as a NIHSS drop of ≥10 points from baseline or NIHSS score of 0 or 1 3. Quality of Life at Day 90 (± 14) assessed by EuroQoL (EQ5D5L)
Primary Procedural Outcome	1. eTICI 2c or greater on first pass as adjudicated by core lab
Secondary Procedural Outcomes	As adjudicated by core lab: 1. eTICI 2b50, eTICI 2b67, eTICI 2c, and/or eTICI 3 on first pass, after primary technique used, and at the end of the endovascular procedure 2. Time from groin puncture to eTICI 2b50, eTICI 2b67, eTICI 2c, and/or eTICI 3 after first pass 3. Overall time from groin puncture to achieve eTICI 2c or 3 and final reperfusion
Safety Outcomes	1. All-cause mortality and stroke-related mortality up to 90 Days (±14) 2. Device and/or procedure related SAEs up to 90 Days (±14) 3. Neurological deterioration at 24 (-6/+24) hours post procedure defined as a NIHSS increase ≥4 points from baseline 4. Symptomatic intracranial hemorrhage (SICH) adapted from European Cooperative Acute Stroke Study (ECASSIII) as any apparent extravascular blood in the brain or within the cranium that is associated with clinical deterioration defined by a NIHSS increase of four points or more from baseline up to 24 (-6/+24) hours 5. Embolization to New Territory adjudicated by core lab
Core Lab Assessments	An independent core lab will adjudicate pre and post-procedure non-invasive imaging and cerebral angiography to include but not limited to:

	• The Alberta Stroke Program Early CT Score (ASPECTS) • Collateral Flow Grade • eTICI Score for Each Pass • Occlusion Location • Pre-procedure Perfusion Assessment • Post-procedure Hemorrhagic Transformation • Embolization to New Territory (ENT) • Vessel Size
Registry Devices	Data will be collected on the use of Stryker market-released neurovascular mechanical access and mechanical thrombectomy devices that are currently available or that may be launched during the conduct of the Registry, including but not limited to: • AXS Infinity LS™ Long Sheath (LS) • AXS Infinity LS™ Plus Long Sheath • FlowGate²™ Balloon Guide Catheter (BGC) • Merci® Balloon Guide Catheter • AXS Catalyst® 5 Distal Access Catheter (DAC) • AXS Catalyst® 6 Distal Access Catheter • AXS Catalyst® 7 Distal Access Catheter • Trevo® Retriever • AXS Vecta™ 71 Aspiration Catheter (Asp Cath) • AXS Vecta™ 74 Aspiration Catheter • Medela Dominant Flex Pump
Device Sizes	All product sizes approved for use by the local regulatory agency
Study Design	
Study Design	This is a prospective, global, consecutive enrollment Registry of anterior circulation acute ischemic stroke patients with a LVO who undergo treatment with one of the interventional techniques using Stryker Neurovascular (SNV) devices for the first pass.
Planned Number of Subjects	Up to 1500 subjects
Planned Number of Sites	Up to 100 sites worldwide
Study Duration	Up to 48 months

<table>
<tr><td>Follow-Up Schedule</td><td>

24 (-6/+24) hours post-index stroke procedure
Discharge/ Day 5-7 (whichever is earlier)
Day 30 (± 14)
Day 90 (± 14)

</td></tr>
<tr><td>Inclusion Criteria</td><td>
1. Subjects who experienced acute ischemic stroke (AIS), eligible for restoration of blood flow using Stryker Neurovascular market-released products in the neurovasculature to remove thrombus
2. Occlusion of intracranial anterior circulation vessel
3. Subject or subject's legally authorized representative (LAR) has signed the informed consent form prior to or within 48 hours post-procedure
4. Subject is willing to comply with the protocol follow-up requirements
5. The intended technique and treated technique must be one of the following techniques for the first thrombectomy pass in the neurovasculature per Instructions For Use (IFU[1]):
<table>
<tr><th>Technique Category</th><th>Devices*</th></tr>
<tr><td>SR Classic</td><td>SR + BGC</td></tr>
<tr><td>SR Combination</td><td>SR + Asp Cath ± Pump + BGC or LS</td></tr>
<tr><td>Direct Aspiration</td><td>Asp Cath ± Pump + BGC or LS</td></tr>
</table>
*Defined devices must be SNV market-released products.
</td></tr>
<tr><td>Exclusion Criteria</td><td>The subject is participating in another device trial or any other clinical trial where the study procedure or treatment might confound this study's endpoint.</td></tr>
<tr><td colspan="2">Statistical Methods</td></tr>
<tr><td>Statistical Test Method</td><td>Sample size is estimated based on the desired measurement precision of primary clinical and procedural outcomes. General summary and descriptive statistics will be used to analyze the study data. Logistic regression will be used to evaluate predictors of good outcomes in each of the techniques. Further details are provided in the Statistical Analysis Plan (SAP).</td></tr>
</table>

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1 INTRODUCTION AND RATIONALE

Worldwide, stroke is the leading cause of death for people above the age of 60 and the fifth leading cause in people aged 15-59, and is the most common cause of chronic adult disability.[2, 3] According to the World Health Organization, approximately 15 million people suffer a stroke annually, about 5 million die, and another 5 million are permanently disabled as a result. On a global scale, stroke claims a life every ten seconds.[6]

Over the course of the past few years, treatment for stroke has rapidly evolved with the current recommendations including both intravenous tissue plasminogen activator (tPA) and endovascular therapy for select patients, based on positive outcomes shown in the five pivotal trials presented in 2014-2015. Goyal et al published the HERMES meta-Analysis which pooled patient-level data to show the additional benefit of endovascular thrombectomy in decreasing disability for patients with large vessel anterior circulation ischemic stroke irrespective of patient characteristics, geographic location, and eligibility for IV tPA.[4] Two other-meta analyses evaluated published randomized clinical trials of endovascular therapy versus standard of care for treatment of LVO AIS and found that endovascular therapy with mechanical thrombectomy resulted in improved functional outcomes for patients compared to standard of care.[5,6]

Evidence also supports that reduced time from symptom onset to reperfusion with endovascular therapies is associated with better clinical outcomes. Most clinical studies in recent years have demonstrated that the faster the time to recanalization or reperfusion, the better the functional outcome for the patient.[7,8,9,10,11] Two factors play key roles in determining time to reperfusion: 1) efficiency and effectiveness of mechanical thrombectomy techniques, and 2) triage, transport and treatment times.

1.1 Mechanical Thrombectomy Techniques

In the context of AIS, endovascular therapy is often considered a single treatment modality; however, it can include a number of different, but related strategies—some of which may be more effective than others.[12,13,14] Common endovascular strategies can include chemical clot dissolution with local delivery of tPA or recanalization of arterial occlusion by clot disruption, aspiration, or retrieval using one or more mechanical devices. Furthermore, the type of mechanical device used and/or the combination of mechanical devices used for endovascular therapy might have a significant influence on reperfusion time and, as a result, functional outcome.[15,16,17] Although newer retrievable stent devices were used in the more recent clinical trials of endovascular therapy, the outcomes of all types of mechanical devices were not recorded in all studies, and few studies evaluated the various ways mechanical devices were used in combination to achieve reperfusion.

The ASSIST Registry is a post-market study, that will focus on the clinical safety and clinical performance of Stryker Neurovascular market released access and mechanical thrombectomy devices. The Registry has been designed to collect data on subjects who have been treated for acute ischemic stroke due to anterior circulation LVO. The Registry will collect data on the following devices (including but not limited to): the AXS Infinity LS Long Sheath, the AXS Infinity LS Plus Long Sheath, the FlowGate[2] and Merci Balloon Guide Catheters (BGC), the AXS Catalyst Distal Access Catheters (DAC), the AXS Vecta Aspiration Catheters, the Trevo Retriever, and the Dominant Flex Medela pump.

Data from subjects treated with the following mechanical thrombectomy techniques will be evaluated. These devices will be evaluated in the context of pre-defined mechanical thrombectomy techniques.

These techniques were chosen to be evaluated based on physician input, current worldwide clinical practice, as well as recent scientific studies of adjunctive therapies performed for AIS. For example, the use of a stent retriever in combination with a BGC ('SR Classic') for the treatment of AIS in the anterior circulation has been shown to improve angiographic results and procedure duration time compared to the use of a stent retriever alone. [16] Furthermore, several studies have demonstrated that the combination of stent retriever and aspiration is safe, fast and effective for first-pass complete reperfusion, [17, 18, 19, 20] and can be more effective than the use of a stent retriever alone.[18] More data are needed to fully understand the various techniques, particularly in relation to safety, effectiveness, and time to reperfusion. This Registry will collect such data to help answer these outstanding questions.

1.2 Triage, Transport and Treatment Times

Improvements in triage, transport and treatment times does play a key role in optimizing functional outcomes for stroke patients.[19,20,21,22,23]In all the major endovascular trials to date, it has been convincingly demonstrated that longer time to initiation of treatment resulted in a worse clinical outcome. [13,17,18,19,20,28] Door to needle times as fast as 20-25 minutes can be achieved with proper planning and infrastructure changes.[24] Strict adherence to stroke performance metrics like door to needle time, imaging-to-puncture, imaging-to-perfusion time and comprehensive metrics like symptom onset to reperfusion time can vastly improve the chances of good clinical outcome.[25,25,26,27]

For example, in the STRATIS Registry using only Solitaire, the median system of care time was 152 minutes, and each hour of delay from this time was associated with a decline in the likelihood of achieving a good outcome for the patient.[28] In addition, Menon and colleagues (2016) reported that imaging to reperfusion time was a significant predictor of outcome in the ESCAPE trial and suggested that inefficiencies in triaging, off-hour presentation, IV tPA administration (if patient was eligible), use of general anesthesia, and endovascular techniques offered major opportunities for improvement in workflow.[29] Finally, the guidelines for the early management of patients with acute ischemic stroke from the American Heart Association and American Stroke Association (2018) strongly recommend streamlined stroke-specific workflows from onset of stroke symptoms to reperfusion of the brain, including faster triage, transport, patient evaluation, imaging, administration of IV tPA (if patient is eligible), and mechanical thrombectomy techniques.[30]

1.3 Quality of Life

The ASSIST Registry will include data on quality of life metrics for subjects treated with mechanical thrombectomy for ischemic stroke due to anterior circulation LVO. These data will allow evaluation of the relationship between mechanical thrombectomy devices and techniques, overall time from symptom onset to recanalization or reperfusion, functional outcomes, and subject-reported quality of life. Understanding these relationships is a critical aspect in optimizing mechanical thrombectomy devices and techniques as well as triage, transport, and treatment times to ensure the best overall quality of life outcome for stroke patients.

1.4 Importance of ASSIST Registry Data

The ASSIST Registry is a global post-market study designed to assess the procedural success and clinical outcomes associated with operator techniques utilizing Stryker Neurovascular Devices used in real-world situations across study sites.

Data collected will include device use and purpose, combinations of devices, mechanical thrombectomy techniques, time from onset to triage, triage to transport, transport to treatment, and overall time from onset to reperfusion as well as quality of life and other valuable data. By collecting and analyzing this information, optimal treatment patterns for select patients can be identified, the critical nature of fastest time possible from symptom onset to reperfusion can be demonstrated, time from onset to reperfusion and all critical steps in between can be streamlined, and more optimal mechanical thrombectomy techniques and devices can be developed.

The data from the ASSIST Registry will have the potential to help us better understand the functional and quality of life outcomes for the millions of individuals around the world who suffer an ischemic stroke each year as well as to ease the global burden of this devastating disease.

2 EXISTING CLINICAL DATA

The principal goal in treating acute ischemic stroke is to restore cerebral blood flow as rapidly and safely as possible. Five clinical studies, the Thrombectomy REvascularization of large Vessel Occlusions (TREVO) in acute ischemic stroke, the TREVO 2 study, the MR CLEAN study, TREVO Registry, and DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN™) Trial were conducted using the Trevo Retriever.

2.1 TREVO Study

The TREVO study was a post marketing prospective, multi-center, single arm study performed at 7 sites in Europe designed to quantify the performance of the Trevo Retriever in providing reperfusion and clinical benefit to subjects experiencing a large vessel occlusion (LVO) within 8 hours of symptom onset.[31] The devices used in the study were the Trevo 4 x 20 mm, Trevo Pro 4, and Trevo 3 x 10 mm.

Sixty (60) subjects were enrolled between February 2010 and August 2011. The primary endpoint was angiographic reperfusion as measured by an independent core lab using the TICI scale. Success was defined as a final TICI score of 2a or better. Post procedure, successful reperfusion was achieved in 91.7% of subjects. In the TREVO study, operators were not restricted from using intra-arterial (IA) lytic, but it was only used in 10% of cases.

In regard to secondary endpoints, 55.0% of subjects achieved 90-day good clinical outcomes (mRS of 0-2), the 90-day mortality rate was 20.0%, the device-related serious adverse event rate was 5.0% and only 5.0% of subjects showed symptomatic intracranial hemorrhage (SICH) at 24 hours.

The TREVO investigational plan pre-defined specific events that were captured to assess safety which included vessel dissection, vessel perforation, intracranial hemorrhage (ICH) (as identified by core lab) and

all deaths. Information for each of these events was collected and then independently adjudicated by the Clinical Events Committee (CEC).

2.2 TREVO 2 Study

The TREVO 2 study was an IDE trial designed to support a 510k application for FDA clearance in the U.S.[18] The trial enrolled 178 subjects between February 3, 2011 and December 1, 2011 at 26 sites in the United States and one site in Spain. The subjects were randomized 1:1 to Trevo (N=88) or Merci (N=90) and were stratified by age and baseline NIHSS to ensure balance in the two arms.

The primary effectiveness endpoint was post-device reperfusion success defined as at least TICI 2a, which was achieved in 86% of patients treated with the Trevo device and 60% of patients treated with the Merci device. The primary safety endpoint was a composite of adverse events. The composite rate for the Trevo device group was 15% and 23% for the Merci device group.

Secondary endpoints included time to reperfusion with a mean time for the Trevo group of 47.8±44.2 minutes and 47.3±38.8 minutes. The 90-day good outcome (mRS 0-2) was 40% for the Trevo group and 22% for the Merci group, and the 90-day mortality rate was 33% for Trevo and 24% for Merci. For the Trevo group 7% of patients had symptomatic ICH at 24 hours and 16% showed neurological deterioration at 24 hours. For the Merci group, 9% had symptomatic ICH at 24 hours and 22% showed neurological deterioration at 24 hours.

Overall the results of the TREVO and TREVO 2 trials demonstrate reperfusion efficacy and safety of the Trevo Retriever.

2.3 MR CLEAN Study

MR CLEAN was a large, prospective, randomized, open label, controlled, multicenter trial in which 16 centers in the Netherlands participated.[32] Subjects with acute ischemic stroke and a proximal intracranial arterial occlusion of the anterior circulation that was confirmed on vessel imaging were randomized to intra-arterial treatment (IAT) plus usual care or usual care alone. The study enrolled 500 subjects at 16 medical centers. A total of 233 subjects were randomized to IAT and 267 subjects to the control group of usual care.

The primary effectiveness endpoint was to demonstrate that IAT plus usual care leads to superior functional independence (mRS $\leq$2) at 90 days compared to usual care alone. There was a shift in the distribution of the primary-outcome scores in favor of the intervention. The adjusted common odds ratio was 1.67 (95% CI, 1.21 to 2.30). The shift toward better outcomes in favor of the intervention was consistent for all categories of the mRS, except for death. Secondary outcomes included: 1) NIHSS score at 24 hours and at 5-7 days/discharge, 2) Barthel index, and 3) EuroQol Group 5-Dimension Self-Report Questionnaire at 90 days. The NIHSS score after 5 to 7 days was, on average, 2.9 points (95% CI, 1.5 to 4.3) lower in the intervention group than in the control group.

This study showed that IAT in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation was effective and safe when administered within 6 hours of stroke onset.

2.4 TREVO Registry

The Thrombectomy REVascularization of large vessel Occlusion (TREVO) Registry is a Stryker Neurovascular Sponsored Registry (data on file) that is a global, multi-center, prospective, open label study. The only requirement of the Registry was to have a confirmed LVO and to use the Trevo Retriever as the initial mechanical thrombectomy device. 2008 subjects across 100 centers had been treated for ischemic stroke with LVO using the Trevo Retriever as the initial mechanical device for thrombectomy. Unlike prior randomized trials, this Registry evaluated all clot locations, including M2 (21.0%) and vertebrobasilar locations (6.9%).

Approximately 3/4 of the patients enrolled in the Registry received treatment within 6 hours of symptom onset; 1/4 received treatment beyond 6 hours. The mean number of passes with the Trevo Retriever was 1.7, with 46.9% of procedures using a balloon guide catheter and 46.6% using an intermediate catheter. The first pass TICI 2b/3 reperfusion rate was 62% and the final TICI 2b/3 reperfusion rate was 93% post procedure. The 90-day mRS 0-2 was 58.6% in the AHA-like cohort, and over 40% of patients showed improvement in NIHSS at 24 hours by 10 points or more.

Data from the TREVO Registry are in line with the recently published HERMES meta-analysis, [33] demonstrating generalizability of the Trevo Retriever in a wide range of real world endovascular cases and techniques.

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

DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN™) Trial was a prospective, randomized, multi-center, open-label trial with a Bayesian adaptive-enrichment design. Subjects were randomized 1:1 to Trevo thrombectomy plus medical management or medical management alone.[34] The study enrolled 206 subjects; 107 in the treatment arm and 99 in the medical management arm. The trial was stopped early due to the results of a pre-specified interim analysis.

The primary objective was 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. The co-primary endpoints were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale) at 90 days. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points: 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999), and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44; posterior probability of superiority, >0.999).

The primary safety outcome was incidence of stroke-related mortality at 90 days. In total, 17% (35/206) of the study subjects had stroke-related mortality within 90 days of enrollment into study: 16% (17/107) in the Treatment Arm and 18% (18/99) in the Control Arm. Stroke-related mortality rates at 90 days did not differ significantly (p= 0.7126) between study arms.

The study concluded that among patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability at 90 days were better with thrombectomy plus standard care than with standard care alone.

3 DESCRIPTIONS OF REGISTRY DEVICES

Stryker market-released neurovascular access and mechanical thrombectomy devices that are currently available or that may be launched during the conduct of the Registry may be included in the ASSIST Registry. Refer to the approved regional Instructions for Use (IFU) for detailed instructions for use, warnings, and precautions.

3.1 Registry Devices

Data will be collected on the use of any Stryker market-released neurovascular access and mechanical thrombectomy devices using the pre-defined registry techniques that are currently available or that may be commercialized during the conduct of the Registry, including but not limited to:

- AXS Infinity LS™ Long Sheath (LS)
- AXS Infinity LS™ Plus Long Sheath
- FlowGate²™ Balloon Guide Catheter (BGC)
- Merci® Balloon Guide Catheter
- AXS Catalyst® 5 Distal Access Catheter
- AXS Catalyst® 6 Distal Access Catheter
- AXS Catalyst® 7 Distal Access Catheter
- Trevo® Retriever
- AXS Vecta™ 71 Aspiration Catheter (Asp Cath)
- AXS Vecta™ 74 Aspiration Catheter
- Medela Dominant Flex Pump

All product sizes approved for use by the local regulatory agency can be used.

3.2 Device Labeling

A copy of the device IFU is included in each device package. Device labels and labeling generally contain the following information as relevant:

- Device dimensions
- Lot number
- Expiration (use before) date
- Compatibility information

4 REGISTRY OBJECTIVE

The purpose of this Registry is to assess the procedural success and clinical outcomes associated with various operator techniques for mechanical thrombectomy in LVO in the anterior circulation.

This Registry will also collect data, including time-to-treatment and quality of life measures, to allow for subset analyses that may be used for regulatory submissions and/or reimbursement dossiers.

4.1 Primary Clinical Outcome

1. Severity of disability at Day 90 (±14) assessed by mRS with a good functional outcome defined as mRS of 0-2 for each technique

4.2 Secondary Clinical Outcomes

1. Excellent functional outcome defined as mRS 0-1 at Day 90 (±14)
2. An "early response" at Discharge/Day5-7 (whichever is earlier) defined as a NIHSS drop of ≥10 points from baseline or NIHSS score of 0 or 1
3. Quality of Life at Day 90 (±14 days) assessed by EuroQoL (EQ5D5L)

4.3 Primary Procedural Outcomes

1. eTICI 2c or greater on first pass as adjudicated by core lab

4.4 Secondary Procedural Outcomes

As adjudicated by core lab:

1. eTICI 2b50, eTICI 2b67, eTICI 2c, and/or eTICI 3 on first pass, after primary technique used, and at the end of the endovascular procedure
2. Time from groin puncture to eTICI 2b50, eTICI 2b67, eTICI 2c, and/or eTICI 3 after first pass
3. Overall time from groin puncture to achieve eTICI 2c or 3 and final reperfusion

4.5 Safety Outcomes

1. All-cause mortality and stroke-related mortality up to Day 90 (±14)
2. Device and/or procedure related SAEs up to Day 90 (±14)
3. Neurological deterioration at 24 (-6/+24) hours post procedure defined as a four or more point increase in NIHSS from baseline
4. Symptomatic intracranial hemorrhage (SICH) adapted from European Cooperative Acute Stroke Study (ECASSIII) as any apparent extravascular blood in the brain or within the cranium that is associated with clinical deterioration defined by a NIHSS increase of four points or more from baseline up to 24 (-6/+24) hours
5. Embolization to New Territory adjudicated by core lab

4.6 Time Points Assessments

The ASSIST Registry will collect data on workflow and procedural information including types of techniques, thrombus location, tandem lesions, and procedure and imaging measurements, along with time specific data points including:

- Last Time Known Well (LTKW)
- First Medical Contact (i.e. 911, Emergency Medical Service)
- Time of Departure from First Hospital if applicable
- Time of Arrival at Treating Hospital
- Time of Arrival at Angiography Suite
- Time of Groin Puncture (Time Skin Punctured by Needle)
- Time of Completion of First Pass
- Time of Reperfusion for eTICI 2b50, eTICI 2b67, eTICI 2c, and/or eTICI 3 after First Pass
- Overall Time to eTICI 2c or 3
- Overall Time of Final Reperfusion

4.7 Core Lab Assessments

An independent core lab will adjudicate pre and post procedure non-invasive imaging and cerebral angiography to include but not limited to:

- The Alberta Stroke Program Early CT Score (ASPECTS)
- Collateral Flow Grade
- eTICI Score for Each Pass
- Occlusion Location
- Pre-procedure Perfusion Assessment
- Post-procedure Hemorrhagic Transformation
- Embolization to New Territory (ENT)
- Vessel Size

5 REGISTRY DESIGN

This is a prospective, global, consecutive enrollment Registry of anterior circulation acute ischemic stroke patients with a LVO who undergo treatment with one of the interventional techniques using SNV devices for the first pass.

5.1 Sites

The Registry will enroll up to 1500 subjects and will be conducted at up to 100 sites worldwide. The Registry devices will have regulatory authorization to be on the market in the geographic location of all sites.

5.2 Duration

The duration of the Registry protocol is approximately 48 months.

5.3 Justification for the Registry Design

The intent of the ASSIST Registry is to collect global data to help compare treatment techniques and promote the criticality of time assessment. Physicians and manufacturers will gain access to valuable information for ongoing improvement in the development of devices focused on the treatment of AIS and for the evaluation of the optimal treatment technique. A new study is required to specifically assess the performance of Stryker products utilizing one of the interventional techniques. The objective of prior studies has focused on safety and effectiveness of Trevo Stent Retriever, and there is limited real-world data regarding treatment techniques that utilize other Stryker Neurovascular devices.

5.4 Method of Enrollment

This Registry has open consecutive enrollment. Clinical data points will be evaluated in all subjects who meet the inclusion/exclusion criteria.

Screening and enrollment information will be maintained electronically in the Electronic Data Capture (EDC) by each site to document basic information such as date screened and reason for screen failures for subjects who fail to meet the study eligibility criteria. To avoid bias, if a center chooses to participate in the ASSIST Registry, every effort should be made to include all thrombectomy cases that follow one of the techniques that use Stryker Neurovascular products performed over a given duration of time in the Registry.

6 STUDY POPULATION

6.1 Selection Criteria

6.1.1 Inclusion Criteria

1. Subjects who experienced acute ischemic stroke (AIS), eligible for restoration of blood flow using Stryker Neurovascular market-released products in the neurovasculature to remove thrombus
2. Occlusion of intracranial anterior circulation vessel
3. Subject or subject's legally authorized representative (LAR) has signed the informed consent form prior to or within 48 hours post-procedure
4. Subject is willing to comply with the protocol follow-up requirements
5. The intended technique and treated technique must be one of the following techniques for the first thrombectomy pass in the neurovasculature per Instructions For Use (IFU).

Table 1. Thrombectomy Techniques to be Evaluated in the ASSIST Registry

Technique Category	Devices*
SR Classic	SR + BGC
SR Combination	SR + Asp Cath ± Pump + BGC or LS
Direct Aspiration	Asp Cath ± Pump + BGC or LS

**Defined devices must be SNV market-released products.*

6.1.2 Exclusion Criteria

The subject is participating in another device trial or any other clinical trial where the study procedure or treatment might confound this study's endpoint.

6.2 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. If a subject chooses to withdraw from the Registry, the reason(s) for withdrawal will be recorded on the appropriate electronic Case Report Form (eCRF) and in the medical record.

6.3 Enrollment Controls

Enrollment will be monitored to ensure that no more than the specified number of subjects is enrolled. The EDC System will be used and monitored to ensure maximum enrollment is contained.

7 STUDY PROCEDURES

7.1 Written Informed Consent

An Informed Consent Form (ICF) template is provided in **Appendix D** for the Investigator to prepare for Institutional Review Board (IRB)/Ethics Committee (EC) submission. The ICF must be prepared in the language(s) of the potential subject population, document version identified, and approved by the site IRB/EC. A copy must be provided to Stryker Neurovascular. Modifications to the form must be approved by Stryker Neurovascular prior to implementation.

An ICF must be obtained pre-procedure or up to 48 hours post- procedure. The ICF must be obtained prior to data entry into the ASSIST Registry EDC. The subject or the subject's legally authorized representative (LAR) will be asked to sign the ICF. Study personnel should document the consent process in the subject's medical record per Good Clinical Practice (GCP). The subject or LAR is to be provided a copy of the signed ICF.

7.2 Pre-Procedure Assessments

The following pre-procedure data will be obtained for subjects enrolled in the Registry:

- Inclusion/Exclusion Criteria
- Informed Consent
- Demographics & Medical History
- Baseline Labs
- Baseline Pre-stroke mRS
- Post-stroke NIHSS assessment
- Stroke Onset
- Neuroimaging (CT, MR)

7.3 Procedure/Treatment

7.3.1 Angiogram Procedure

For subjects enrolled in this Registry, treatment initiation will be defined as the date and time of groin puncture.

A diagnostic angiogram must be performed to determine the appropriate procedural technique to be used for reperfusion. The following will be collected for subjects enrolled in the Registry:

- The occlusion location(s)
- A single image when all devices are in position for each pass. This will be the start time of the pass. *Please note: A single image must be performed, even if there is failure to access the clot*.
- Angiographic evaluations with clear visualization of the target artery before treatment initiation, after each attempt to remove thrombus from the occlusion location, and post-procedure to determine vessel patency. It is considered best practice to utilize the same angiographic orientation before and after device use as well as post-procedure and to include late venous phase in the angiogram acquisition to allow a valid analysis of the reperfusion status of the vessel(s).
- Expanded TICI scores for each pass within the vascular territory being treated. Time of eTICI assessment will be the stop time of each pass.

Sites will submit <u>all</u> de-identified angiographic data for subjects enrolled in the Registry, 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 de-identified angiography dataset.

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

7.3.2 Thrombectomy Procedure

The thrombectomy techniques that will be evaluated in the ASSIST Registry are included in Table 2. Additionally, Table 3 includes examples of SNV devices that can be used for each technique. Note that not all devices in Table 3 have market approval in all global regions for the intended use as described in Table 2. Physicians should use each device according to the intended use statement in the most current version of the IFU with regards to the devices' intended use, compatibility, preparation and the recommended retrieval procedure.

Table 2. Procedural Techniques Evaluated in the ASSIST Registry

Technique	Description
SR Classic	**Definition:** Referred to as the "SR Classic" technique which combines a BGC for proximal flow control and retrieval with the Trevo Retriever.
	Procedural technique: The BGC is placed at the desired location. Using a guide wire, a microcatheter is then navigated through the BGC to the site of occlusion. Position the microcatheter tip distal to the thrombus and remove the guidewire. The retriever is delivered through the microcatheter and is deployed per IFU and is allowed to expand and integrate into the clot. Prior to retriever retraction, the BGC is inflated (to control antegrade flow in the ICA). During retrieval, it is recommended that aspiration is applied through the BGC per the Trevo IFU.
SR Combination	**Definition:** Referred to as the "SR Combination" technique which involves using distal aspiration applied at the clot in conjunction with proximal flow control and a stent retriever.
	Procedural technique: The BGC or LS is placed at the desired location. Using a guide wire, the aspiration catheter and microcatheter are navigated to the site of the occlusion – the aspiration catheter may be left proximal to the occlusion until retrieval begins. Position the microcatheter tip distal to the thrombus and remove the guidewire. The retriever is delivered through the microcatheter and is deployed per IFU. The retriever is allowed to expand and integrate into the clot and microcatheter is removed. *[For BGC Only: Prior to retriever retraction, the BGC is inflated (to control antegrade flow in the ICA).]* Aspiration is initiated and the aspiration catheter is navigated proximal to the clot. Aspiration is applied through the aspiration catheter and when there is no blood flow it has engaged the thrombus. The retriever and aspiration catheter are retracted together with care being taken not to bring the retriever all the way into the aspiration catheter.
Direct Aspiration	**Definition:** Referred to as the "Direct Aspiration" technique which involves aspiration through the aspiration catheter.
	Procedural technique: The BGC or LS is placed at the desired location. Using a guidewire, the aspiration catheter is navigated to the occlusion using the appropriate delivery catheter. Before aspiration, remove the delivery catheter and guidewire. Aspiration is applied through the aspiration catheter.

Table 3. Examples of Technique Products

Technique Category	Technique	Products
SR Classic	1	SR (Trevo) + BGC (FlowGate^2 or Merci)
SR Combination	2	SR (Trevo) + Asp Cath (AXS Catalyst DAC, Vecta) ± Pump + LS (AXS Infinity LS, AXS Infinity LS Plus)
	3	SR (Trevo) + Asp Cath (AXS Catalyst DAC) ± Pump + BGC (FlowGate^2 or Merci)
Direct Aspiration	4	Asp Cath (AXS Catalyst DAC, Vecta) ± Pump + LS (AXS Infinity LS, AXS Infinity LS Plus)
	5	Asp Cath (AXS Catalyst DAC) ± Pump + BGC (FlowGate^2, Merci)

Note: Additional SNV products that are commercialized during the conduct of the Registry may also be included.

7.4 24 hours (-6/+24) Post Procedure

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

- NIHSS
- Imaging (CT, MR)
- Device and/or Procedure Related AEs
- All SAEs
- All Deaths

Any death or device and/or procedure related AEs and all SAEs should be reported to Stryker Neurovascular within 24 hours of becoming aware by eCRF completion. Available information regarding the primary cause of death and date/time of death will be recorded.

7.5 Discharge/Day 5-7 (whichever is earlier)

A subject may be discharged from the hospital at the Investigator's discretion. The following data will be collected between Day 5-7 (if subject remains in the hospital) or at discharge, whichever occurs first:

- mRS
- NIHSS
- Device and/or Procedure Related AEs
- All SAEs
- All Deaths

Any death or device and/or procedure related AEs and all SAEs should be reported to Stryker Neurovascular within 24 hours of becoming aware by eCRF completion. Available information regarding the primary cause of death and date/time of death will be recorded.

7.5.1 Post Discharge Follow Up

The designated staff at the clinical site will review the follow-up schedule with the subject to maximize compliance. 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 after all subjects have completed the Day 90 (± 14) follow-up assessments or have discontinued the study early. Requirements of each follow-up evaluation are detailed below.

7.6 Day 30 (±14 days)

At Day 30 (± 14 days) the following study assessments should be performed:

- mRS (A telephone assessment may be conducted, but in-person is strongly encouraged)
- Device and/or Procedure Related AEs
- All SAEs
- All Deaths

Any death or device and/or procedure related AEs and all SAEs should be reported to Stryker Neurovascular within 24 hours of becoming aware. 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.

7.7 Day 90 (±14 days)

At Day 90 (± 14 days) the following study assessments should be performed:

- mRS (A telephone assessment may be conducted, but in-person is strongly encouraged)
- EuroQol (EQ5D5L)
- Device and/or Procedure Related AEs
- All SAEs
- All Deaths

Any death or device and/or procedure related AEs and all SAEs should be reported to Stryker Neurovascular within 24 hours of becoming aware. 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.

Table 4. Time and Events Schedule

Time and Events Schedule						
Assessments:	**Pre-procedure (Screening /Baseline)**	**Procedure**	**24 (-6/+24) hrs. post procedure**	**Discharge (or Day 5-7 whichever comes first)**	**Day 30 ±14 days**	**Day 90 ±14 days**
Inclusion/Exclusion Criteria	✔					
Informed Consent*	✔					
Demographics & Medical History	✔					
Baseline Labs	✔					
mRS**	✔			✔	✔	✔
NIHSS Assessment	✔		✔	✔		
EuroQol (EQ5D5L)						✔
Stroke Onset	✔					
CT/MR[ɣ]	✔		✔			
Angiogram Procedure Information [‡***ɣ]		✔				
Hospital Stay/Discharge Disposition****				✔		
Adverse Events[‡]		✔	✔	✔	✔	✔
Study Completion						✔

*Written Informed Consent must be obtained prior to subject enrollment and any data entry.
**Telephone mRS assessment is acceptable if subject is not able to return in person.
***See study binder for worksheets listing items to record during the procedure.
****Study Staff should review the study requirements with the subject and arrange all follow-up visits at discharge.
‡ All AEs during procedure, only Device Related and/or Procedure Related AE & all SAE, death post procedure.
ɣ CT/MR and Angiographic images will be de-identified with subject ID# if submitted to SNV or the core lab.

8 STATISTICAL METHODS

8.1 Sample Size Estimate and Justification

The sample size of ASSIST is based on the precision of the estimate of functional independence (90-day mRS 0-2) in a real-world setting. The TREVO Registry had an observed rate of 55.3% with a 95% CI of [53.1, 57.4] for functional independence and the rate is similar to that reported in a pooled analysis of 5 RCT thrombectomy trials (46.0%)[7]. Given the uncertainty of outcomes of some of the procedural techniques a rate of 50% functional independence was assumed for this study with a precision of 6%. With a 95% Wald

confidence interval of [47%, 53%], a sample size of 1200 observes such precision inference with a probability > 0.9. A 20% loss to follow-up increases the total sample size to 1200/0.8 = 1500.

There may not be uniform recruitment of patients to each technique group. Thus, a maximum of 5 groups was used to calculate the minimum and maximum sample size per group, given that additional techniques and commercialized devices may be added during the conduct of the study. Assuming a minimum group size of 72 and a total enrollment of 1500, the maximum enrollment in any technique group is (1500 – 72) / 4 = 357.

The overall sample size as well as minimum and maximum enrollment per technique provides sufficient sample size to provide precise estimates of the study endpoints in each of the procedural techniques.

8.2 Statistical Analysis

Day 90 outcomes will be compared to pre-stroke mRS status, baseline imaging and time of symptom onset to treatment. Interim analysis will be performed periodically, and the results will be reported. Additional interim analyses and data reporting will occur throughout the study enrollment period.

Sub-group analyses for the Registry will be performed under guidance from the Study PIs, Steering Committee, and Sponsor.

General summary and descriptive statistics will be used to analyze the data. For each binary and categorical variable, procedural success, the point estimate, percentage, and its exact 95% confidence interval will be provided. For continuous variables, total sample size, mean, standard deviation, median, minimum, and maximum will be provided.

Logistic regression will be used to evaluate predictors of good outcomes in each of the techniques.

Further details will be provided in the SAP.

All statistical analyses will be performed using SAS version 9.4 or above. (Copyright © 2002-2008 by SAS Institute Inc., Cary, North Carolina, USA, all rights reserved)

9 DATA MANAGEMENT

9.1 Data Collection and Processing

Data will be collected in a secure, password protected electronic data capture (EDC) system, which is accessible via the Internet. All pertinent data will be entered by trained study center personnel into the electronic Case Report Forms (eCRFs). A unique subject ID number will be assigned to each subject enrolled. 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 the sponsor or may be identified and queried during the routine remote monitoring process. Remote monitoring may be performed to verify data accuracy and ensure queries are resolved. The Principal Investigator must ensure the accuracy and completeness of the recorded data and provide his/her electronic signature on the appropriate eCRF.

If images are sent to a Core Lab, the results may also be entered into the EDC system and 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 Lab for appropriate resolution.

10 MONITORING

Stryker Neurovascular will assess each participating site to assure that the Investigator(s) understand the protocol, as well as their obligations to conduct the Registry in accordance with applicable Regulations, GCP's and the Registry protocol. The monitor will also confirm that the Investigator has an adequate subject population, facilities, personnel and time to conduct the Registry properly. While the Sponsor intends to use remote monitoring methods, periodic on-site monitoring visits will be made to confirm that the site remains compliant with the protocol, applicable regulations, GCP and that all agreed-upon activities are carried out by the Investigator and other specified staff members.

Data will be monitored on-site and/or remotely for completeness and logical consistency. De-identified procedure summary and ASSIST Registry worksheets sent to Stryker Neurovascular must have the subject identification number recorded on any forms. The procedure documents for each subject enrolled may be compared against the eCRFs to ensure consistency.

It is important that the Investigator and relevant study site personnel are available during 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 Registry eCRFs. This access must be disclosed to the subject via the informed consent.

11 AUDITING

Sites may be subject to a quality assurance audit by Stryker Neurovascular or its designees, or other regulatory authorities.

12 ADVERSE EVENTS

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or persons, whether or not related to the medical device(s). All subjects will be assessed for complications or adverse events during the procedure and at all follow-up visits per section 7.4-7.7, and recorded on the AE case report form. Data to be collected will include the AE event term, onset and resolution dates (or whether the AE is ongoing), seriousness, management/treatment, outcome, and determination of the relationship to the devices and the index procedure. All AEs will be followed until resolution or an appropriate endpoint is reached, or until the subject has completed or discontinued the registry.

More specifically, the following adverse events are to be reported on the Adverse Event case report form:

- All AEs and serious adverse events (SAE) that occur during the procedure
- Only device and/or procedure related AEs post procedure through Day 90
- All SAEs post procedure through Day 90

NOTE: Any "prolonged" hospitalization(s) related to the study procedure which is considered standard of care due to subject age, co-morbidities or neurological status at presentation will not be considered SAEs

- Any event causing neurological deterioration defined as a ≥ 4 point increase on the NIHSS from baseline (e.g. cerebral edema, brain herniation, stroke progression) which is related to the index stroke
- Any event causing symptomatic intracranial hemorrhage (SICH) defined as a ≥ 4 point increase in NIHSS from baseline for which the hemorrhage is determined to be the cause
- All device-related adverse events (also known as "adverse device effects" [ADEs])
- All serious adverse device effects (SADEs)
- All unanticipated serious adverse device effects (USADEs)
- All adverse events that result in death through Day 90

  NOTE: Death should not be recorded as the AE term but should be reflected as an outcome to a specific AE

Pre-treatment findings and pre-existing medical conditions will not be reported as AEs unless there is an increase in their frequency or severity during the course of the registry. Elective/planned hospitalization after enrollment in the Registry will not be regarded as an AE or a SAE. However, AEs that may occur during elective hospitalization, and are unrelated to the elective hospitalization should be evaluated and recorded appropriately.

12.1 Adverse Event Definitions and Classification

Term	Definition	Reference
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject, users or other persons, whether or not related to the investigational medical device	ISO 14155:2011
Adverse Device Effect (ADE)	Any adverse event related to the use of a medical device. *Note 1*: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. *Note 2*: This definition includes any event resulting from use error or intentional misuse of the device	ISO 14155:2011
Serious Adverse Event (SAE)	An adverse event that: • led to death, or • 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 or prolonged hospitalization, or • resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or • led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE	ISO 14155:2011
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event	ISO 14155:2011
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report	ISO 14155:2011

12.2 Relationship

The Investigator must assess the relationship of the AE to each Stryker Neurovascular device using the following criteria categories and definitions:

- Unrelated - The AE is due to a concurrent illness or effect of another device/drug and is not related to the study device.
- Related - The AE is due to the study device (possible, probable, or highly probable).

All AEs that are related to a Stryker device will be reported to the Stryker Neurovascular Complaint Management Center prompting a further investigation. Sites will be contacted for more detailed information.

The Investigator must assess the relationship of the AE to the index procedure using the following categories and definitions:

- Unrelated - The AE is due to a concurrent illness or effect of a drug and is not related to the index procedure.
- Related - The AE is due to the index procedure (possible, probable, or highly probable).

12.3 Reporting Requirements

Any death or device and/or procedure related AEs and all SAEs should be reported within 24 hours of becoming aware to Stryker Neurovascular via data entry into the eCRFs. If access to eCRFs is not available, then the information can be emailed to ASSISTRegistry@Stryker.com.

12.4 Device Failures, Malfunctions, and Product Nonconformities

All Stryker Neurovascular product failures, malfunctions and product nonconformities will be documented on the appropriate eCRF, and the involved device(s) should be returned to Stryker Neurovascular for analysis if possible. Assistance with returning the study device(s) can be provided by contacting your local Customer Service Center. Contact information for Customer Service Centers is located in the Regulatory Binder. Device failures and malfunctions should also be documented in the subject's medical record.

All Stryker Neurovascular device failures, malfunctions and product nonconformities should be reported within 24 hours of becoming aware to Stryker Neurovascular via data entry into the eCRFs. If access to eCRFs is not available, then the information can be emailed to ASSISTRegistry@Stryker.com.

NOTE: Stryker Neurovascular device failures, malfunctions and product nonconformities should be reported as soon as possible after becoming aware of them and are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF. All Stryker device failures, malfunctions, product nonconformities and resulting AEs are reported to the Stryker Neurovascular Complaint Management Center prompting a further investigation. Sites will be contacted for more detailed information.

12.5 Reporting to Regulatory Authorities / IRBs / ECs Investigators

Stryker Neurovascular is responsible for reporting adverse event information to all participating Investigators and regulatory authorities, as applicable.

Any adverse event associated with the use of Stryker Neurovascular products will be reported in accordance with the European Medical Device Directive MDD 93/42/EEC and MEDDEV 2.12-1 Guidelines on a Medical Device Vigilance System, and local regulatory requirements.

The Site PI is responsible for informing the IRB/EC of any events as required by local procedure. A copy of this report may be requested by Stryker Neurovascular.

13 RISK BENEFIT ANALYSIS

The risks associated with this study are limited to a possibility that confidential patient information may be disclosed. It is possible that subjects enrolled into the ASSIST Registry will receive no direct benefit from participation. Possible benefits of the Registry include providing information regarding the use of the procedural techniques that involve Stryker Neurovascular study devices; (i.e.the AXS family of products, the FlowGate^2 and Merci Balloon Guide Catheters, Trevo Retriever, and the Medela Dominant Flex Pump) that may benefit future patients, as well as a better understanding of Quality of Life after a thrombectomy procedure.

13.1 Risk Minimization

In order to minimize risks, Stryker Neurovascular will carefully select study sites and Investigators who have experience with neuro-interventional procedures. Thorough training on the protocol, IFU and Registry requirements will be conducted and Stryker Neurovascular will be available to address any Registry specific issues or questions. Reasonable measures will be taken to minimize any risk of loss of confidentiality including the use of subject ID numbers for data entry and de-identification of any images or records sent to the core-lab or Stryker. A Steering Committee will assist in oversight of the ASSIST Registry. Safety monitoring of the data will be continuous throughout the Registry.

14 STEERING COMMITTEE

The ASSIST Registry Global Steering Committee will include the ASSIST Registry Global PIs and up to 12 members. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

15 ETHICAL CONSIDERATIONS

15.1 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.

15.2 Institutional Review Board / Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material (if applicable) must be submitted to the IRB/EC for written approval. A copy of the written IRB/EC initial approval of the protocol and ICF must be received by Stryker Neurovascular before recruitment of subjects into the ASSIST Registry. Approval from the IRB/EC for all subsequent protocol amendments and changes to the ICF must be on file with Stryker. Investigational sites must notify the IRB/EC of any events per local regulations.

15.3 Protocol Adherence

Prior to beginning the study, the Investigator must sign the Investigator Agreement agreeing 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.

Stryker Neurovascular will ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

16 STUDY ADMINISTRATION

16.1 Pre-Study Documentation Requirements

Prior to enrolling any subjects into the Registry, the site must complete all pre-study essential documents, and these must be confirmed to be on file with the Stryker Neurovascular, including but not limited to: CV, medical license, W-8 or W-9 (where applicable), signed clinical trial agreement, IRB/EC approval of the study and the Informed Consent and all required study training. A site initiation visit will be conducted prior to authorization to enroll. No site may begin enrolling subjects until they receive written approval from Stryker Neurovascular.

16.2 Record Retention

The Investigator will maintain all essential Registry documents and source documentation, in original format, that support the data collected on the study subjects in the event that the data is necessary for regulatory submission. Documents must be retained for 2 years or longer per local governing regulatory guidelines.

16.3 Criteria for Suspending/Terminating a Study Center

Stryker Neurovascular reserves the right to stop or suspend a study center at any time after site authorization to enroll if no subjects have been enrolled within 6 months, or if there are concerns with data integrity.

17 REFERENCES

1. SNV Product IFU: https://www.strykerneurovascular.com/us/products/access

2. CDC. Stroke Facts. Sep 2017; Available from: http://www.cdc.gov/stroke.facts.htm.

3. http://www.worldstrokecampaign.org/learn/facts-and-figures.html.

4. Goyal M, Menon BK, Zwam WH, et al.; Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016; p 1723-31. https://doi.org/10.1016/S0140-6736(16)00163-X.

5. Kennedy SA, Baerlocher MO, et al.; Meta-Analysis of Local Endovascular Therapy for Acute Ischemic Stroke, J Vasc Interv Radiol.; 2016 Mar; p 307-21.

6. Badhiwala JH, Nassiri F; Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis; JAMA; 2015 Nov 3; p 1832-43.

7. Doerr M, et.al; Evaluation of Strategies to Reduce Time to Revascularization in Acute Ischemic Stroke; International Stroke Conference Poster Abstract; Stroke 2017; 48:AWP411.

8. Darazanli C, Consoli A, Labreuche J, et al.; Impact of Modified TICI 3 versus 2b Reperfusion Score to Predict Good Outcome following Endovascular Therapy; AJNR Am J Neuroradiol. 2017 Jan; p 90-96.

9. Appireddy RM, Demchuk AM, Goyal M, et al.; Endovascular Therapy for Ischemic Stroke; J Clin Neurol.; 2015 Jan; p 1-8.

10. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; p 1019 –30 CrossRef Medline.

11. Turk 2014 AS, Turner R, Spiotta A, et al.; Comparison of Endovascular Treatment Approaches for Acute Ischemic Stroke: Cost Effectiveness, Technical Success, and Clinical Outcomes; J Neurointerv Surg. 2015 Sep; p 666-70; doi 10.1136/neurintsurg-2014-01182. Epub 2014 Jul 15; PMID: 25028502.

12 . Gupta R, Vora A, Horowitz M, et al.; Multimodal Reperfusion Therapy for Acute Ischemic Stroke Factors Predicting Vessel Recanalization; Stroke. 2006; p 986-990; DOI: 10.1161/01.STR.0000209303.02474.27.

13. 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; p 1241-1249.

14. Nogueira, R.G., Lutsep, H.L., Gupta, R., et al., Trevo versus Merci Retrievers for Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischaemic Stroke (TREVO 2): A Randomised Trial. Lancet, 2012. 280: p 1231-40.

15. Coutinho J, Liebeskind,D; Slater L-A, et al.; Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic Stroke: A Pooled Analysis of the SWIFT and STAR Studies; JAMA Neurol 2017; p 268-274; DOI:10.1001/jamaneurol.2016.5374.

16. Lapergue B, Blanc R, Gory B, et al.;Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER Randomized Clinical Trial.; JAMA. 2017 Aug 1; p 443-452. DOI: 10.1001/jama.2017.9644; PMID:28763550

17. Sivan-Hoffmann R, Gory B, Rabilloud M, et al.; Patient Outcomes with Stent-Retriever Thrombectomy for Anterior Circulation Stroke: A Meta-Analysis and Review of the Literature; Isr Med Assoc J. 2016 Sep; p 561-566

18. Madjidvar J, Hermes J, Freitag-Wolf S, et al.; Stent-thrombus Interaction and the Influence of Aspiration on Mechanical Thrombectomy: Evaluation of Different Stent Retrievers in a Circulation Model; Neuroradiology 2015 Aug; p 791-7; DOI: 1007/s00234-015-1526-4; Epub 2015 Apr 24; PMID: 25903428.

19. Middleton S, Levi C, Dale S, et al.; Triage, Treatment and Transfer of Patients with Stroke in Emergency Department Trial (the T3 Trial): A Cluster Randomised Trial Protocol; Implement Sci, 2016 Oct; p 139; PMID 27756434.

20. Goyal M, Jadhav AP, Bonafe A, et al. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke; Radiology; 2016 p. 888-897; DOI: 10.1148/radiol.2016160204.

21. Grotta JC, Savitz SI, Persse D; Stroke Severity As Well As Time Should Determine Stroke Patient Triage; Stroke 2013 Feb; p 555-7; doi: 10.1161/STROKE AHA.112669721, Epub 2013 Jan 3; PMID: 23287779.

22. Audebert HJ, Saver J, Starkman S, et al.; Prehospital Stroke Care: New Prospects for Treatment and Clinical Research; Neurology 2013 Jul 30; p 501–508; doi: 10.1212/WNL.0b013e31829e0fdd; PMID PMC3776535.

23. Mosley I, Nicol M, Donnan G, Patrick I, Kerr F, Dewey H. The impact of ambulance practice on acute stroke care. Stroke. 2007; p 2765–2770.

24. Meretoja A, Mustanoja S. Tatlisumak T, et al.; Reducing In-Hospital Delay to 20 Minutes in Stroke Thrombolysis; Neurology 2012 Jul; p 306-13; DOI: 10.1212/WNL.0b013e31825d6011. Epub 2012 May 23; PMID: 22622858.

25. Jadhav A, Kenmuir C, Aghaebrahim A, et al.; Interfacility Transfer Directly to the Neuroangiography Suite in Acute Ischemic Stroke Patients Undergoing Thrombectomy; Stroke. **2017**; 48:00-00. DOI: 10.1161/. STROKEAHA.117.016946.

26. McTaggart RA, Yaghi S, Cutting SM, et al.; Association of a Primary Stroke Center Protocol for Suspected Stroke by Large-Vessel Occlusion with Efficiency of Care and Patient Outcomes; JAMA Neurol. 2017 Jul 1; p 793-800; doi: 10.1001/jamaneurol.2017.0477; PMID: 28492918.

27. Schlemm L, Ebinger M, Nolte C, Endres M; Impact of Prehospital Triage Scales to Detect Large Vessel Occlusion on Resource Utilization and Time to Treatment; Stroke 2018; 49:00-00; DOI: 10.1161/STROKEAHA.117.019431.

28. Mueller-Kronast NH, et al.; Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke: Primary Results of the STRATIS Registry; Stroke. 2017 Oct; p 2760-2768; Epub 2017 Aug 22.

29. Menon B K, et al., Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (**ESCAPE**) Randomized, Controlled Trial, Circulation. 2016 Jun 7;133, p 2279-86, Epub 2016 Apr 13.

30. Powers W J, et al., June 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke (AIS) Regarding Endovascular Treatment, Stroke, October 2015, p 3020-3035.

31. Wahlgren, N., Macho, J. Killer M., Liebeskind D., Jansen, O. Final Results from the Trevo Study (Thrombectomy Revascularization of large Vessel Occlusions in acute ischemic stroke). International Stroke Conference, 2012.

32. Berkhemer OA, Fransen PSS, Beumer D, et al.; A randomized trial of intraarterial treatment for acute ischemic stroke; N Engl J Med 2015;372:11-20; [PMID: 25517348].

33. Goyal M, Menon BK, van Zwam WH, et al.; Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials; Lancet 2016; 387:1723-31; [PMID: 26898852].

34. Nogueira R, Jadhav A, Haussen D, et al.; Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct (DAWN Trial); N Engl J Med 2018; 378; p 11-21; January 4, 2018

18 APPENDICES

Appendix A. Abbreviations

Abbreviation/Acronym	Full Term
AE	Adverse Event
AHA	American Heart Association
AIS	Acute Ischemic Stroke
Carotid T	Distal terminus of the carotid artery
CATO	Conventional Angiography Target Occlusion
CRA	Clinical Research Associate
CRF	Case Report Form
CSA	Clinical Study Agreement
CT	Computed Tomography
CTA	Computed Tomography Angiography
DRSAE	Device-related SAE
DSA	Digital Subtraction Angiography
ECASIII	European Cooperative Acute Study Stroke Study III
eCRF	electronic Case Report Form
eTICI	(expanded) Thrombolysis in Cerebral Infarction
EQ5D5L	EuroQol Questionnaire – 5 Level 5D Version
GCP	Good Clinical Practices
IA	Intra-Arterial
IAT	Intra-Arterial Therapy
ICH	Intracranial Hemorrhage
ID	Identification
IFU	Instructions For Use
IV	Intravenous
IV tPA	Intravenous tissue Plasminogen Activator
LAR	Legally Authorized Representative

Abbreviation/Acronym	Full Term
LTKW	Last Time Known Well
LVO	Large Vessel Occlusion
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
PI	Principal Investigator
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAH	Subarachnoid Hemorrhage
SICH	Symptomatic Intracranial Hemorrhage
t-PA	Tissue Plasminogen Activator
UADE	Unanticipated Adverse Device Effect

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 requiring additional treatment such as blood transfusion or surgical repair.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or untoward clinical sign (including abnormal laboratory results) in subjects, users, or other persons. NOTE - This definition does not imply that there is a relationship between the adverse event and the device under investigation.

At Risk Tissue-Volume: Differentiate tissue at risk, but salvageable, from tissue that is already infarcted and at risk for hemorrhage with reperfusion

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.

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

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

Embolization to New Territory (ENT): Embolization into a previously uninvolved area of the brain associated with new ischemic changes on 24-hour postprocedural CT or MR imaging. For example, 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.

Groin Puncture: Time Skin Punctured by Needle.

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

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

Intraprocedure Mortality: Death occurring during the index thrombectomy procedure

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

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

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. 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 ≤ 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.

Pass (Start Time and Stop Time):

Start Time is the time of the single image performed when all devices are in position for each pass.

Stop Time is the time of the eTICI assessment completed after the pass.

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.

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 protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

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

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

- NOTE 2 – Elective/planned hospitalization after the study procedure will not be regarded as an AE or a SAE. However, AEs that may occur during elective hospitalization, and are unrelated to the elective hospitalization should be evaluated and recorded appropriately.

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

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

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

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

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

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

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

Unanticipated Serious Adverse Device Effects (USADEs): Any serious adverse effect on health or safety, 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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 localized contrast extending outside the vessel lumen.

Appendix C. Expanded TICI (eTICI) Perfusion Categories

- Grade 0: Equivalent to no reperfusion or 0% filling of the downstream territory.
- Grade 1: Reflects thrombus reduction without any reperfusion of distal arteries.
- Grade 2a: Reperfusion in less than half or 1–49% of the territory.
- Grade 2b50: 50–66% reperfusion
- Grade 2b67: 67-89% reperfusion
- Grade 2c: 90–99% reperfusion
- Grade 3: Complete or 100% reperfusion

Reference

Liebeskind DS, Bracard S, Guillemin F, et al eTICI reperfusion: defining success in endovascular stroke therapy Journal of NeuroInterventional Surgery Published Online First: 07 September 2018. doi: 10.1136/neurintsurg-2018-014127

Appendix D. Informed Consent Form Template