Study Protocol

Study Title:

Envi™-SR **R**andomized **C**ontrolled **T**rial for Endovascular Treatment of Ischemic Stroke

NCT Number:
NCT05107206

Protocol Number:
CL-001 Rev. D

Date:
February 19, 2021

3 Jenner, Suite 100 | Irvine, CA 92618 USA | +1.949.258.9946

NeuroVascTechnologies.com

ENVI RCT

Envi™-SR Randomized Controlled Trial for Endovascular Treatment of Ischemic Stroke

Clinical Investigation Protocol

Study Identification: NV-001

Document: CL-001 – Revision D

This Document is Confidential and Proprietary

Study Sponsor:

NeuroVasc Technologies, Inc.

3 Jenner, Suite 100

Irvine, CA 92618 USA

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REVISION HISTORY

Revision	Date	Change
A	01MAR2020	Initial draft for IDE submission to FDA
B	22JUL2020	Revisions to address FDA feedback on original IDE G200131
C	07DEC2020	Revisions to address FDA feedback from Q-sub meeting Q201563/S001 on 15OCT2020
D	19FEB2021	Revisions to address FDA feedback from FDA conditional approval letter

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SIGNATURE PAGE

To be signed and returned to Sponsor, prior to study initiation.

Study Title:	**ENVI RCT** Envi™-SR Randomized Controlled Trial for Acute Ischemic Stroke Treatment
Investigational Device:	Envi™-SR
Sponsor Study ID:	NV-001
Sponsor:	NeuroVasc Technologies, Inc.
Document Title:	ENVI RCT Clinical Investigation Protocol
Document and Revision:	CL-001 Rev. D

I,_____,
(name of principal investigator)

_____,
(Specialty, e.g. anesthesiology, neurosurgery or other discipline)

at the_____,
(name of hospital)

the undersigned, attest that I have read and understood this Protocol and agree on its content and to abide by the above-mentioned version and any subsequent amendments during my participation in the evaluation. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant parts of the International Conference of Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), ISO 14155:2011, 21 CFR Part 11, 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 812, 21 CFR Part 820, the Declaration of Helsinki, and the pertinent individual country laws/regulations.

_____ _____

Principal Investigator Signature Date

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the design and specific provisions of this Institutional Review Board (IRB)/ Ethics Committee (EC)/ Research Ethics Board (REB) approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Conference of Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), ISO14155:2011, ISO 13485:2016, 21 CFR Part 11, 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR 812, 21 CFR Part 820, 93/42/EEC MDD and the applicable local, state, or national regulatory/legal requirement(s). The Principal Investigators will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB/EC/REB, except where necessary to eliminate an immediate hazard(s) to the study subjects. The Principal Investigators will promptly report to the IRB/EC/REB and the Sponsor of any changes in research activity and all unanticipated problems involving risk to human subjects, or others, as required.

Sponsor Approval

Clinical Protocol CL-001 Revision D is approved by the Sponsor:

Michael Losordo Chief Operating Officer	Date

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- Representatives of the Competent Authority (i.e., government agency having regulatory jurisdiction) of the country (or countries) in which the study is to be conducted.
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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASPECTS	Alberta Stroke program early CT score
AVM	Arteriovenous Malformation
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
CT	Computed Tomography
CTA	Computed Tomography Angiogram
DALYS	Disability-life adjusted years
DMC	Data Monitoring Committee
eCRF	Case Report Form
EDC	Electronic Data Capture
ENT	Embolization of New Territory
eTICI	Expanded Thrombolysis in Cerebrovascular Infarction
FDA	Food and Drug Administration
FMEA	Failure Mode and Effect Analysis
FPE	First Pass Effect
GCP	Good Clinical Practice
HI	Hemorrhagic infract
IA t-PA	Intra-arterial tissue plasminogen activator
ICA	Internal Carotid Artery
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICH	Intracranial Hemorrhage
IDE	Investigational Device Exemption
IFU	Instructions for Use
ITT	Intention-to-treat
IV	Intravenous
IV t-PA	Intravenous tissue plasminogen activator
LAR	Legally Authorized Representative
LVO	Large vessel occlusion
MCA	Middle Cerebral Artery
mFPE	Modified First Pass Effect
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
mTICI	modified Thrombolysis in Cerebrovascular Infarction

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NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Score
PH	Parenchymal hematoma
PI	Principal Investigator
PP	Per Protocol
PRSAE	Procedure Related Serious Adverse Event
PT	Preferred Term
PTAE	Pretreatment Adverse Event
RFA-A	Rankin Focused Assessment-Ambulation
RHV	Rotating Hemostasis Valve
SAE	Serious Adverse Event/Experience
SADE	Serious Adverse Device Effect
SIV	Site Initiation Visit
SOC	System Organ Class
SOP	Standard Operating Procedure
SQV	Site Qualification Visit
TEAE	Treatment Emergent Adverse Event
TFSO	Time from Stroke Onset
TICI	Thrombolysis in Cerebrovascular Infarction
TIMI	Thrombolysis in Myocardial Infarction
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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PROTOCOL SYNOPSIS

Study Title	**ENVI RCT** Envi™-SR Randomized Controlled Trial for Endovascular Treatment of Ischemic Stroke
Sponsor	**NeuroVasc Technologies Inc.** 3 Jenner, Suite 100, Irvine, CA 92618, USA
Principal Investigator(s)	**Vitor Mendes-Pereira, MD, MSc** Division of Neuroradiology - Joint Department of Medical Imaging Division of Neurosurgery - Department of Surgery Toronto Western Hospital - Krembil Brain Institute - University Health Network Professor of Medical Imaging and Surgery University of Toronto Lead Scientist - RADIS lab: Research in Cerebral Vascular Diseases Toronto Western Hospital - 3MCL-436 399 Bathurst St. Toronto, ON, M5T 2S8 Email: Vitor.Pereira@uhn.ca Tel: 1.416.603.5800 (ext.: 5564)
	Raul G Nogueira, MD Director, Neuroendovascular Service Marcus Stroke & Neuroscience Center Grady Memorial Hospital Professor of Neurology, Neurosurgery and Radiology Emory University School of Medicine Grady Memorial Hospital 80 Jesse Hill Jr Drive SE Room# 8D108A Atlanta, GA 30303 Email: raul.g.nogueira@emory.edu Tel: 1.404.616.4013
Study Sites	A current list of sites will be maintained in the Sponsor's study files.

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Core Laboratory Director	**David S Liebeskind, MD, FAAN, FAHA, FANA, FSVIN, FWSO** Professor of Neurology Director, Outpatient Stroke and Neurovascular Programs Director, UCLA Cerebral Blood Flow Laboratory Director, UCLA Vascular Neurology Residency Program UCLA Department of Neurology Director, Neurovascular Imaging Research Core Director, UCLA Stroke Center President-Elect, Society of Vascular and Interventional Neurology (SVIN) President, American Society of Neuroimaging (ASN) Neuroscience Research Building 635 Charles E Young Drive South, Suite 225 Los Angeles, CA 90095-7334 Email: davidliebeskind@yahoo.com Tel: 1.310.963.5539
Medical Monitor	**Thanh Nguyen, MD, FRCPc, FSVIN, FAHA** Director, Neuroendovascular Service Professor of Neurology, Neurosurgery & Radiology Boston Medical Center Boston University School of Medicine FGH Building, 3rd Floor 820 Harrison Avenue Boston, MA 02118 Email: Thanh.Nguyen@bmc.org Tel: 1.617.638.4282
Investigational Device	Envi™-SR
Study Type	Interventional (Clinical Trial)
Primary Purpose	Treatment
Study Design	The study is designed as a prospective, multinational, randomized, parallel group-controlled, blinded, non-inferiority study.
Masking	Double (patient, outcomes assessor)
Treatment Arms	Subjects who meet the inclusion criteria will be randomized in a 1:1 ratio to one of the following two treatment arms: Arm one (1): Endovascular Treatment with Envi™-SR Arm two (2): Endovascular Treatment with an FDA cleared device for treatment of acute ischemic stroke (Control Devices)
Study Objective	The study objective is to examine and compare clinical outcomes, as measured by Modified Rankin Scale (mRS) at 90 days (± 15 days) post treatment, and related performance characteristics of the Envi™-SR and concurrent parallel Control Devices currently cleared by the U.S. FDA for treatment of stroke.
Estimated Enrollment	Adaptive design with a target ITT sample size of 270 subjects (135 per arm) with a maximum of 560 subjects to be enrolled.

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Sites	Up to 30 sites in United States, Canada, and Europe
Indications for Use	Study Reports summarizing data from this investigation will be submitted to the FDA as part of an IDE application seeking the following indications for use: 1. The Envi™-SR is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). Endovascular therapy with the device should be started within 6 hours of symptom onset. 2. The Envi™-SR is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV t-PA or who fail IV t-PA therapy are candidates for treatment. 3. The Envi™-SR is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50 cc for age < 80 years, 0-20 cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.
Device Description	The Envi™-SR is a self-expanding, nitinol stent-like mechanical thrombectomy device that is designed to be delivered to the neurovasculature through a microcatheter to retrieve thrombus.
Duration of Study	The total duration of the study is expected to be approximately 36-48 months
Duration of Subject Participation	Subjects will be in study for up to 90 days (± 15 days).
Primary Effectiveness Endpoint	The proportion of subjects with good clinical outcome defined as Modified Rankin Score (mRS) of ≤2 as assessed by a blinded assessor at 90 days (± 15 days).
Primary Safety Endpoint	Device-related or procedure-related symptomatic intracranial hemorrhage (sICH) defined by the Heidelberg Bleeding Classification at 24 hours (-8/+12 hours) (as read by the Core Lab and adjudicated by Clinical Events Committee (CEC)).

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Safety Endpoints	The following endpoints will be presented for each treatment arm as part of the safety analysis: 1. Symptomatic intracranial hemorrhage (sICH) defined by the Heidelberg Bleeding Classification post-procedure (as read by the Core Lab and adjudicated by the CEC). 2. Asymptomatic intracranial hemorrhages (aICH) defined by the Heidelberg Bleeding Classification within 24 (-8/+12) hours post procedure (as read by the Core Lab and adjudicated by the CEC). 3. Device and Procedure Related Serious Adverse Events (PRSAE) within seven (7) days (-2/+3 days) or discharge, whichever is sooner. 4. Device and Procedure Related Serious Adverse Events (PRSAE). 5. Device-related Serious Adverse Device Effects. 6. Procedure-related mortality at seven (7) days (-2/+3 days) or discharge, whichever is sooner. 7. Stroke-related mortality at 90 days (±15 days) post-procedure. 8. All-cause mortality at 90 days (±15 days) post-procedure. 9. Neurological deterioration – defined by an increase of four (4) points or more on the NIHSS score, at the time of diagnosis compared to immediately before worsening within seven (7) days (-2/+3 days) or discharge, whichever is sooner.
Secondary Effectiveness Endpoints	The following secondary effectiveness endpoints will be described and compared between the two (2) treatment arms: 1. The first secondary effectiveness endpoint will be an assessment of the mRS shift from baseline at 90 days (± 15 days) following the study index procedure. 2. The second secondary effectiveness endpoint will be an assessment of the proportion of subjects who achieve reperfusion measured using the expanded Thrombolysis in Cerebrovascular Infarction index (eTICI). Successful achievement of the endpoint is defined as achieving an eTICI score of 2b50 or greater [eTICI 2b50-3] in the target vessel following three or less passes of the randomized device (as adjudicated by Core Lab). 3. The third secondary effectiveness endpoint will be an assessment of the proportion of subjects in whom a successful First Pass Effect is achieved. Successful achievement of the endpoint is defined as achieving an eTICI First Pass Effect (FPE) defined as eTICI 2c-3 after a single pass (as adjudicated by Core Lab). 4. The fourth secondary effectiveness endpoint will be an assessment of the proportion of subjects in whom a successful Modified First Pass Effect is achieved. Successful achievement of the endpoint is defined as achieving an eTICI Modified First Pass Effect (mFPE) defined as eTICI 2b50-3 after a single pass (as adjudicated by Core Lab). 5. The fifth secondary effectiveness endpoint will be an assessment of the proportion of subjects with Early Response defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1 at seven (7) days (-2/+3 days) or discharge, whichever is sooner.

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Pre-specified Tertiary (Exploratory) Endpoints	The tertiary endpoints of the study will include, but are not limited to the following: 1. The first exploratory endpoint will be the proportion of subjects with excellent clinical outcome defined as Modified Rankin Score (mRS) of ≤1 as assessed by a blinded certified assessor at 90 days (± 15 days) post treatment. 2. The second exploratory endpoint will be an assessment of reperfusion based on the multinomial eTICI score (as adjudicated by the Core Lab). 3. The third exploratory endpoint will be an assessment of the infarct growth as determined by the change in ASPECTS between baseline and 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab). 4. The fourth exploratory endpoint will be an assessment of the infarct growth as determined by the change in lesion volumes measured by MR/CT perfusion imaging between baseline and 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab, in subject subset with MR/CT perfusion imaging at 24 hours). 5. The fifth exploratory endpoint will be an assessment of final infarct volume at 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab, in subject subset with MR/CT perfusion-weighted imaging at 24 hours). 6. The sixth exploratory endpoint will be an assessment of the time to restoration of flow (i.e. time from arterial puncture to initial restoration of flow; time from arterial puncture to eTICI 2b50 or better, time from first angiogram to initial restoration of flow, time from first angiogram to eTICI 2b50). 7. The seventh exploratory endpoint will be an assessment of Device Technical Success, defined as the proportion of devices with which successful delivery, deployment, and recapture of the randomized device is achieved. 8. The eighth exploratory endpoint will be an assessment of the number of passes to reperfusion of eTICI 2b50. 9. The ninth exploratory endpoint will be an assessment of the number of passes to final result. 10. The tenth exploratory endpoint will be an assessment of the number of passes to achieve reperfusion of eTICI 2b50 or greater (as adjudicated by the Core Lab). 11. The eleventh exploratory endpoint will be an assessment of the proportion of subjects who experience embolization of new territory (ENT) (as adjudicated by the Core Lab). 12. The twelfth exploratory endpoint will be an assessment of the proportion of subjects who experience embolization distal to the target occlusion (as adjudicated by the Core Lab). 13. The thirteenth exploratory endpoint will be the NIHSS Total Score as a continuous measure at each observation time point and change from baseline. NIHSS Total Score will be presented for the entire NIHSS scale and excluding scores on the Aphasia Subscale. 14. The fourteenth exploratory endpoint will be an assessment of the proportion of subjects with vessel patency based on MRA or CTA at 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab, in subject subset with MRA/CTA imaging at 24 hours).

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Inclusion Criteria	1. Clinical signs consistent with acute ischemic stroke 2. Pre-stroke Modified Rankin Score ≤ 2 3. Age 18 years and no upper limit (patient must be 18 years old at time of consent). 4. NIHSS ≥ 6 at the time of randomization 5. Subject is able to start treatment (defined as time of arterial puncture) within 24 hours of stroke onset or last known well and within 90 minutes from last baseline CT/ MRI. 6. Imaging: For strokes in the anterior circulation the following imaging criteria should also be met: a. If stroke onset (as defined by the time the patient was last seen at baseline) is within 6 hours: Baseline ASPECTS ≥6 on non-contrast CT (NCCT) or DWI-MRI; b. If stroke onset is within 6-24 hours, advanced imaging with either CT perfusion or DWI-MRI is required. Baseline infarct volume must be ≤50cc for patients under 80 years old and ≤20cc for patients 80 years or older. 7. Location: Angiographic confirmation of an occlusion of an ICA (including T or L occlusions), M1 or M2 MCA, with eTICI flow of zero (0) – one (1). 8. Patients for whom IV t-PA is indicated are treated with IV t-PA without delay. 9. IV t-PA, if used, is initiated within three (3) hours of stroke onset (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the subject has received/is receiving the correct IV t-PA dose for the estimated weight. 10. Consent: The patient or the patient's legally authorized representative (LAR) has signed and dated an Informed Consent Form. 11. Will comply with protocol follow-up schedule. 12. Patient was ambulatory prior to stroke, i.e. able to walk without another person's assistance.

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Exclusion Criteria	1. Life expectancy likely less than six (6) months. 2. Females who are pregnant or breastfeeding. 3. Known history of severe allergy (more than rash) to contrast medium that cannot be medically controlled. 4. Suspicion of renal failure (Renal failure as defined by a serum creatinine >3.0 mg/dL (264 µmol/L) or Glomerular Filtration Rate (eGFR) <30). 5. Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg) NOTE: If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled. 6. Currently participating in another interventional (drug, device, etc.) research project that may confound the results of this study. 7. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency. (A subject without history or suspicion of coagulopathy does not require INR or prothrombin time lab results to be available prior to enrollment.) 8. Known history of platelet count <100,000/µL. 9. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol). 10. Subjects with occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation). 11. CT or MR evidence of hemorrhage. 12. Seizures at stroke onset. 13. Suspicion of aortic dissection. 14. Patients with known hypersensitivity to nickel-titanium. 15. Evidence of dissection in the extra or intracranial cerebral arteries. 16. Stenosis, or any occlusion, in a proximal vessel that requires treatment or prevents access to the site of occlusion. 17. Presumed septic embolus, suspicion of bacterial endocarditis, or other serious infection. 18. Suspected cerebral vasculitis based on medical history and CTA/Magnetic Resonance Angiogram (MRA). 19. Excessive vascular access tortuosity that will likely prevent endovascular access. 20. Baseline CT or Magnetic Resonance Imaging (MRI) showing intracranial tumor (except asymptomatic small meningiomas less than three (3) cm). 21. Significant mass effect with midline shift 22. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies three months prior to use of treatment device 23. Unlikely to be available for 90-day (± 15 days) follow-up (e.g. no fixed home address, visitor from overseas). 24. Rapid neurological improvement prior to study enrollment suggesting resolution of signs/symptoms of stroke such as a decrease that leads to an NIHSS below the study cut-off of six (6). 25. Patient has suffered a hemorrhagic or ischemic stroke or TIA in at least the last three (3) months. 26. Patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, mRS score at baseline must be ≤ 2. This excludes patients who are severely demented, require constant assistance in a nursing home type setting or who live at home but are not fully independent in activities of daily living (toileting, dressing, eating, cooking and preparing meals, etc.). 27. Known cancer with metastases. 28. Subject currently uses or has a recent history of illicit drug(s), which includes marijuana. 29. Recent past history (within three (3) months) or clinical presentation of intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), ruptured arteriovenous malformation (AVM) or ruptured aneurysm.

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	30. The patient is in a coma.

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Statistics	This prospective, multi-center randomized adaptive clinical study is composed of three (3) phases: screening, procedure, and follow-up. The analyses to address the primary and secondary objectives will be based on the data collected during the procedure and follow-up period. There is a single primary effectiveness endpoint and a primary safety endpoint. There are five (5) secondary endpoints that will be evaluated statistically in hierarchical order. The results from the fourteen tertiary endpoints will be summarized and compared between the two (2) randomized treatment arms as supportive information. The non-inferiority margins for the primary and secondary endpoints come from five (5) published reference studies using retrieval devices in a similar subject population. Where a non-inferiority margin is not available from the peer-reviewed literature, the confidence limit of the difference (Envi™-SR minus Control) in the proportion of subjects experiencing the event of interest, establishing non-inferiority will require zero to be contained within the 1-sided 97.5% or 2-sided 95% confidence limits. The target Intention to Treat (ITT) sample size for this clinical investigation is 270 subjects: 135 subjects per arm. An interim assessment based on conditional power (CP) will be performed by the independent Data Monitoring Committee (DMC) after 50% of the target ITT enrollment (135 subjects) has been randomized and either completed the 90-day (±15 days) evaluation visit or withdrawn prematurely. The interim assessment may result in the target enrollment being increased to a maximum of 560 subjects consented and enrolled. Following the interim assessment, the DMC will provide a non-binding recommendation to the sponsor to either continue enrolling to the target sample size, increase enrollment up to the maximum sample size, or stop the study for futility (CP<37%). At the time of the interim assessment performed by the DMC, the Committee will receive data on all adverse events, effectiveness, investigational site, time last seen well (TLSW), and Additional Therapy for each patient. Through inspection of the tabulated data the DMC will be tasked with examining if data are consistent with planning estimates as described in the DMC Charter. The Intention to Treat (ITT) population will include all subjects that have signed the informed consent form (ICF) and were randomized. The primary population for the primary and secondary analyses for this study will be the ITT population. The ITT population will also serve as the Safety population. Randomization to either Envi™-SR or Control will be performed in a 1:1 ratio, stratified by six (6) factors using a dynamic randomization scheme: • Age: ≥67 and <67 • Site of occlusion: ICA, MCA M1, MCA M2 • Baseline/Enrollment NIHSS score: <17 and ≥17 • Prior IV t-PA usage: Yes and No • Time to symptom onset: ≥6 hours and <6 hours • Baseline ASPECTS: 6-7 and 8-10 This randomized study will ensure that the assessing clinical team are blinded to treatment assignment. Due to the nature of the treatment, and access to the patient records, the treatment team is not required to be blinded. The treatment team will obtain a randomization assignment using a web-based randomization system. The primary effectiveness and safety endpoints will be evaluated simultaneously. If the primary effectiveness endpoint is met (Envi™-SR non-inferior to Control), the secondary effectiveness endpoints will be evaluated statistically in the hierarchical order presented in this protocol and the Statistical Analysis Plan (SAP).

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	The primary effectiveness endpoint is an assessment of global disability assessed via the blinded evaluation by the assessing clinical team of the proportion of subjects with a Modified Rankin Scale (mRS) ≤ 2 recorded 90 days (±15 days) after the study index procedure. The proportions will be compared between the Envi™-SR and Control device arms. The variability between and within the five (5) peer-reviewed reference studies serves as the basis for establishing the non-inferiority margin for this endpoint. The primary effectiveness endpoint will be derived three (3) ways: Method 1: mRS based on the observed results, independent of the use of additional therapies to retrieve the clot. Multiple imputation will be used to impute the mRS score for patients who become lost to follow-up prior to the 90 day evaluation. Method 2: mRS based on the observed results for patients where additional therapies were not used to retrieve the clot. Patients who required additional therapy for reperfusion failure or additional off-label therapies to retrieve the clot will be automatically treated as primary effectiveness endpoint failures. Multiple imputation will be used to impute the mRS score for patients who become lost to follow-up prior to the 90 day evaluation. Method 3: mRS based on the observed results for patients where additional therapies were not used to retrieve the clot. Subjects who required any additional therapy, either on label or off-label, to retrieve the clot will be automatically treated as primary effectiveness endpoint failures. Multiple imputation will be used to impute the mRS score for patients who become lost to follow-up prior to the 90 day evaluation. Method 1 is the primary method for the derivation of the primary effectiveness endpoint for the study; Method 2 and Method 3 represent secondary derivations of the primary effectiveness endpoint. The non-inferiority margin for the primary effectiveness endpoint has been pre-specified at 12.5%. The primary effectiveness analysis will be based on the lower bound of the 1-sided 97.5% confidence interval of the difference (Envi™-SR minus Control) in global disability. If the lower bound is numerically greater than -12.5%, Envi™-SR will be considered non-inferior to Control. The primary safety endpoint is an assessment of device-related or procedure-related symptomatic intracranial hemorrhage (sICH) within 24 hours (-8/+12 hours) (as read by the Core Lab and adjudicated by CEC) of the study index procedure. The incidence of sICH is not expected to exceed 4% in either arm of the study. If the upper bound of the 1-sided 97.5% confidence interval of the difference (Envi™-SR minus Control) in sICH is numerically less than 7%, Envi™-SR will be considered non-inferior to Control.

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1. Introduction

In the simplest terms, a stroke is an interruption of blood flow to the arteries in the brain. Sometimes called a “heart attack” of the brain, time to tissue reperfusion is the critical factor for prognosis and final patient outcome. Just like coronary flow interruptions, a stroke may be caused either by a blockage (clot) in the blood vessel (ischemic stroke), or bleeding due to a rupture or perforation of the affected vessel (hemorrhagic stroke).

It is estimated that worldwide, eighty percent of all strokes are ischemic in nature.[2] Acute ischemic stroke (AIS) is considered the first, second or third leading cause of death worldwide.[2] The World Health Organization predicts that disability-life adjusted years (DALYS) from stroke will rise from 38 million in 1990 to over 60 million by the year 2020. Globally up to 15 million people will suffer a stroke, with 5.9 million stroke related deaths and 10.2 million DALYs lost. In Europe, the reported incidence of stroke in men varies from 101.1 to 239.3 per 100,000, to 63.0 to 158.7 per 100,000 in women. Ischemic stroke accounts for the majority of all strokes, among which 8-12% result in death within the first 30 days. In the US, the costs of stroke are estimated by the National Institute of Health to exceed $73 billion annually.[3] Known risk factors and predictors of stroke include cardiac comorbidities (arrhythmias), chronic hypertension, physical inactivity, larger waist-to-hip ratios, elevated lipid levels, and histories of diabetes, smoking, increased alcohol intake and psychosocial stress and/or depression.[2]

Ischemic strokes contribute to significant morbidity and mortality worldwide, especially in developed countries. More than eight in 10 strokes happen because an artery becomes blocked, causing a sudden loss of blood flow to part of the brain.[4] Damage to brain tissue will occur initially in the region contiguous to the blocked artery (the so-called *“infarct core”*), while a *“penumbra”* of at-risk tissue surrounding this region remains viable for some time following onset of stroke and with timely intervention may respond to efforts to restore blood flow to the region.

Ischemic strokes can be due to large-vessel atherosclerosis, aorto-cardioembolism, small-vessel occlusion, other determined causes, and undetermined causes. Acute ischemic stroke due to large vessel occlusion (LVO)-vertebral, basilar, carotid terminus, middle and anterior cerebral arteries- likely portends a worse prognosis than stroke unassociated with LVO.[5]

The large vessels of the brain include the Internal Carotid Artery (ICA), Middle Cerebral Artery (MCA), Anterior Cerebral Artery (ACA), Vertebral Artery (VA), and the Basilar Artery (BA). Occlusion of these large arteries in ischemic stroke is associated with significant disability and mortality. Revascularization of intracranial arterial occlusions is the therapeutic goal in stroke therapy. Endovascular mechanical revascularization (thrombectomy) is an increasingly used method for intracranial large vessel recanalization in acute stroke. Currently, a number of mechanical recanalization devices are in clinical use. First generation devices included the Merci Retriever device. Second generation devices based on stent-like technology, referred to as “Stentrievers®,” “stent-retrievers”, “stent retrievers,” or simply “retrievers” are currently the standard of care for treatment of LVO and acute ischemic stroke in a defined subset of AIS patients.

The Envi™-SR has been developed and CE marked in Europe for revascularization in patients experiencing AIS. The Envi™-SR is approved for use in the US strictly within the confines of the NV-001 Study. In this study the Envi™-SR is intended for use in the neurovasculature per the indications listed below.

1. The Envi™-SR is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA).

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Endovascular therapy with the device should be started within 6 hours of symptom onset.

2. The Envi™-SR is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV t-PA or who fail IV t-PA therapy are candidates for treatment.
3. The Envi™-SR is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50 cc for age < 80 years, 0-20 cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.

1.1. Background

1.1.1. Intra-Venous and Intra-Arterial Thrombolytics

Currently, IV lytics are used in Europe and the United States for patients presenting up to 4.5 hours after symptom onset. Although in the US IV tissue plasminogen activator (t-PA) is indicated for use in patients presenting up to 3 hours after symptom onset, US national clinical practice guidelines[2] recommend administering IV lytics in the 3-4.5 hours window to those patients who meet the ECASS 3 study inclusion/exclusion criteria.[6 7]

In addition to time constraints, IV thrombolytic therapy has been demonstrated to be less effective in recanalizing proximal occlusions of large vessels, such as the ICA and MCA. Since a large percentage of strokes presenting at hospitals are large vessel occlusions, this is an important clinical challenge to address. Additionally, not all patients may be treated with thrombolytic therapy, and so mechanical thrombectomy is a valuable alternative in patients contraindicated for t-PA or where t-PA treatment is not effective.

Direct arterial infusion of thrombolytic agents was first introduced in the late 1990's and has been shown to have moderate recanalization success rates in smaller vessels when administered within 1-4 hours of the event. Intra-arterial infusion of thrombolytic agents is not currently indicated in the US.

1.1.2. Bridging Therapy

Acute stroke treatment protocols vary by hospital center. CT or other imaging is used to exclude hemorrhagic stroke, and CTA (CT Angiography) or MR is used to confirm Large-Vessel Occlusion. Additional imaging assessment, such as use of MRA and/or CT Perfusion, varies by center. Since the presentations of clinical results from the MR CLEAN[8 9], ESCAPE[10 11], SWIFT PRIME[12], EXTEND-IA[13], and REVASCAT[14] studies and ARISE II[15], many centers have adopted a bridging approach to treatment – immediately starting an IV dose of lytics, then transferring the patient to the angiography suite of a comprehensive stroke center as quickly as possible to speed the time to intra-arterial intervention, if needed. Bridging therapy should occur as determined appropriate by the physician and local practice guidance.[9 13-18]

1.1.3. Ethical Considerations – Global

The Envi™-SR device is not cleared in either the U.S. by the FDA or in Canada by Health Canada. It is an investigational device that may be used in the U.S. and Canada within the confines of the NV-001 Study. The purpose of this IDE Study is to gather information on device effectiveness, safety, and performance to support an application for clearance to FDA and Health Canada.

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For subjects enrolled in European study sites, the Envi™-SR device will be used according to the investigational indications for use per the instructions for use. It is an investigational device that may be only used within the confines of the NV-001 Study. The collection and analysis of the data requires ethical approval.

The intent of the NV-001 Study is to collect data on subjects in a prospective manner; all subjects who are screened and meet all Inclusion/Exclusion criteria will be included in the analysis. Coded subject data in the form of angiographic and CT and/or MRI images, and completed case report forms are required in order to assess the study endpoints. Informed consent will be sought from the subjects or their legal representative for participation and to give permission for the sponsor and subcontractors (Contract Research Organization (CRO), Clinical Events Committee (CEC), Data Monitoring Committee (DMC), and Core Lab) to have access to these data.

Physicians should follow local practice guidance's, their own routine best practice, requirements per this protocol, and the Envi™-SR or control device's instructions for use, when participating in the study.

2. Investigational Device Description

2.1. General Description

The Envi™-SR is a self-expanding, nitinol stent-like mechanical thrombectomy device that is designed to be delivered to the neurovasculature through a microcatheter to retrieve thrombus.

The device is intended for use in the neurovasculature in the ICA, and the M1 and M2 segments of the middle cerebral artery (MCA).

The Envi™-SR is intended for use by physicians trained in neurointerventional catheterization and the treatment of ischemic stroke. After access through the site of vessel occlusion is obtained, the Envi™-SR is delivered endovascularly through a microcatheter under fluoroscopic guidance in a similar manner to that of other neurovascular stent retrievers. Once across the site of vessel occlusion, the stent-like element of the device is deployed and the microcatheter can be removed. If a proximal flow regulation device like a balloon guide catheter (BGC) has been placed proximal to the clot, the BGC is inflated to restrict antegrade flow just prior to retrieval. The Envi™-SR is then retrieved with the clot while applying aspiration to the guide catheter or BGC, restoring blood flow.

The device is available in nine (9) sizes from 3 x 10 mm to 5 x 55 mm as described in Table 2.1.

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Table 2.1: Envi™-SR Product Specifications and Recommended Sizing Guidelines							
REF	Envi™-SR Labeled Sizing Diameter x Length (mm)	Recommended Vessel Diameter (mm)		Expanded Device Diameter (mm)	Retriever Delivery Wire Length (cm)		Fluoromarker location (cm) (maximum distance from Retriever tip to fluoromarker start)
		Min.	Max.		As-supplied (without extension)	With extension	
FG-004-001-US	**3x10**	**2.0**	**3.0**	3.5	200	340	135
FG-004-002-US	**3x15**				200	340	136
FG-004-003-US	**3x20**				200	340	137
FG-004-014-US	**4x25**	**2.0**	**4.0**	5.0	205	340	138
FG-004-016-US	**4x35**				205	340	139
FG-004-018-US	**4x45**				205	340	140
FG-004-035-US	**5x30**	**2.5**	**5.0**	6.0	205	340	139
FG-004-037-US	**5x40**				205	340	140
FG-004-039-US	**5x55**				205	340	141

The working portion of the device is a nitinol retrievable stent-like assembly mounted on the distal end of a delivery wire, as shown in **Figure 2-1**. Platinum/tungsten coils at the distal end of each segment, the proximal end of the working length, and the delivery wire allow for visualization during fluoroscopy.

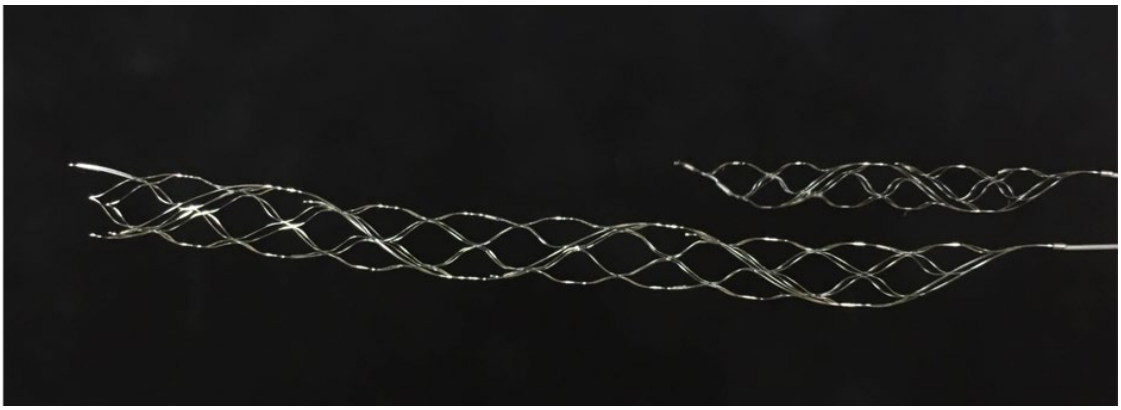

Figure 2-1: Envi™-SR 3x20 and 5x55 stent-like element

2.1.1. Description of Accessories

The Envi™-SR includes the Retriever component, an introducer sheath, extension wire, and two wire handgrips. These components are packaged together within the same pouch.

2.1.2. Packaging Configuration

The Envi™-SR sterile barrier system is comprised of a Tyvek and polymeric pouch. The Retriever is contained in a dispenser coil and sealed within the pouch. The pouch is placed into a carton along with the Instructions for Use (IFU) and the carton is sealed with a carton seal. This is the only packaging configuration for the Envi™-SR.

2.1.3. Study Device Labeling

The Envi™-SR labeling consists of a carton and pouch label, and Instructions for Use (IFU). Labeling is consistent with 21 CFR 812.5(a) and includes the name and place of business of the manufacturer, packer or distributor, the quantity of contents, and the following statement: “CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use.” The labeling describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. The device label contains device

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dimensions, part and lot number, and an expiration date.

2.2. Compatibility

• The Envi™-SR 3mm Retrievers are compatible with microcatheters with an inner diameter of 0.0165 inch (0.42mm) or larger.

• The Envi™-SR 4mm and 5mm Retrievers are compatible with microcatheters with an inner diameter of 0.021 inch (0.53mm) or larger.

Non-clinical compatibility testing has been performed for the Envi™-SR 3mm Retrievers with the Excelsior® SL-10® and Echelon™-14 microcatheters, and for the Envi™-SR 4mm and 5mm Retrievers with the Rebar™-18 microcatheter.

• The Retriever has a visual marker (“fluoromarker”) on the delivery wire. When the fluoromarker nears the microcatheter Rotating Hemostatic Valve (RHV) it indicates the distal end of the device is nearing the end of the microcatheter. Based on this fluoromarker location, the Envi™-SR Retrievers are recommended for use with microcatheters 135cm or longer.

• Based on non-clinical testing, the Envi™-SR Retrievers are recommended for use with a guide / intermediate catheter with a minimum inside diameter .057 inch or an 8-9F balloon guide catheter with a minimum inside diameter of .078 inch.

Refer to the instructions supplied with all interventional devices and materials to be used in conjunction with the Envi™-SR for their intended uses, contraindications and potential complications.

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3. Study Objective

The study objective is to examine and compare clinical outcomes, as measured by Modified Rankin Scale (mRS) at 90 days (± 15 days) post treatment, and related performance characteristics of the Envi™-SR and concurrent parallel Control Devices currently cleared by the U.S. FDA for treatment of stroke.

3.1. Primary Endpoints

The primary effectiveness endpoint is the proportion of subjects with good clinical outcome defined as Modified Rankin Score (mRS) of ≤2 as assessed by a blinded assessor at 90 (± 15) days post treatment.

The primary safety endpoint is the proportion of subjects with device-related or procedure-related symptomatic intracranial hemorrhage (sICH) at 24 hours (-8/+12 hours) post treatment defined by the Heidelberg Bleeding Classification[19] as read by the Core Lab and adjudicated by the CEC.

3.2. Secondary Effectiveness Endpoints

The following secondary effectiveness endpoints will be described and compared between the two treatment arms:

1. The first secondary effectiveness endpoint will be an assessment of the mRS shift from baseline at 90 days (± 15 days) following the study index procedure.
2. The second secondary effectiveness endpoint will be an assessment of the proportion of patients who achieve reperfusion measured using the expanded Thrombolysis in Cerebrovascular Infarction index (eTICI). Successful achievement of the endpoint is defined as achieving an eTICI score of 2b50 or greater [eTICI 2b50-3] in the target vessel following three or less passes of the randomized device (as adjudicated by Core Lab).
3. The third secondary effectiveness endpoint will be an assessment of the proportion of patients who achieve a successful First Pass Effect. Successful achievement of the endpoint is defined as achieving an eTICI First Pass Effect (FPE) defined as eTICI 2c-3 after a single pass (as adjudicated by Core Lab).
4. The fourth secondary effectiveness endpoint will be an assessment of the proportion of patients who achieve a successful Modified First Pass Effect. Successful achievement of the endpoint is defined as achieving an eTICI Modified First Pass Effect (mFPE) defined as eTICI 2b50-3 after a single pass (as adjudicated by Core Lab).
5. The fifth secondary effectiveness endpoint will be an assessment of the proportion of subjects with Early Response defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1 at seven (7) days (-2/+3 days) or discharge, whichever is sooner.

3.3. Pre-specified Tertiary (Exploratory) Endpoints

The pre-specified tertiary (exploratory) endpoints of the study will consist of the following. Additional exploratory endpoints may be evaluated.

1. The first exploratory endpoint will be the proportion of subjects with excellent clinical outcome defined as Modified Rankin Score (mRS) of ≤1 as assessed by a blinded certified assessor at 90 days (± 15 days) post treatment.
2. The second exploratory endpoint will be an assessment of reperfusion based on the multinomial eTICI score (as adjudicated by the Core Lab).

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3. The third exploratory endpoint will be an assessment of the infarct growth as determined by the change in ASPECTS between baseline and 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab).
4. The fourth exploratory endpoint will be an assessment of the infarct growth as determined by the change in lesion volumes measured by MR/CT perfusion imaging between baseline and 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab, in patient subset with MR/CT perfusion imaging at 24 hours).
5. The fifth exploratory endpoint will be an assessment of final infarct volume at 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab, in patient subset with MR/CT perfusion-weighted imaging at 24 hours).
6. The sixth exploratory endpoint will be an assessment of the time to restoration of flow (i.e., time from arterial puncture to initial restoration of flow; time from arterial puncture to eTICI 2b50 or better, time from first angiogram to initial restoration of flow, time from first angiogram to eTICI 2b50).
7. The seventh exploratory endpoint will be an assessment of Device Technical Success, defined as the proportion of devices with which successful delivery, deployment, and recapture of the randomized device is achieved.
8. The eighth exploratory endpoint will be an assessment of the number of passes to reperfusion of eTICI 2b50.
9. The ninth exploratory endpoint will be an assessment of the number of passes to final result.
10. The tenth exploratory endpoint will be an assessment of the number of passes to achieve reperfusion of eTICI 2b50 or greater (as adjudicated by the Core Lab).
11. The eleventh exploratory endpoint will be an assessment of the proportion of patients who experience embolization of new territory (ENT) (as adjudicated by the Core Lab).
12. The twelfth exploratory endpoint will be an assessment of the proportion of patients who experience embolization distal to the target occlusion (as adjudicated by the Core Lab).
13. The thirteenth exploratory endpoint will be the NIHSS Total Score as a continuous measure at each observation time point and change from baseline. NIHSS Total Score will be presented for the entire NIHSS scale and excluding scores on the Aphasia Subscale.
14. The fourteenth exploratory endpoint will be an assessment of the proportion of subjects with vessel patency based on MRA or CTA at 24 hours (-8/+12 hours) post treatment (as adjudicated by the Core Lab, in patient subset with MRA/CTA imaging at 24 hours).

3.4. Safety Endpoints

All reports of Adverse Events (AE)s will be classified according to System Organ Class (SOC) and Preferred Term (PT) using the MedDRA coding system. All AEs will be provided to the DMC for review at DMC meetings. The CEC will adjudicate all AEs of Special Interest. The CEC adjudication of severity and relatedness of the event to the device, procedure and/or disease state will be used for final tabulations.

The following endpoints will be presented to the DMC for each treatment arm as part of the safety analysis and adjudicated by the CEC:

0. (1° Primary) Device-related or procedure-related symptomatic intracranial hemorrhage (sICH) at 24 hours (-8/+12 hours) post treatment defined by the Heidelberg Bleeding Classification

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1. Symptomatic intracranial hemorrhage (sICH) defined by the Heidelberg Bleeding Classification post-procedure (as read by the Core Lab and adjudicated by the CEC).
2. Asymptomatic intracranial hemorrhages (aICH) defined by the Heidelberg Bleeding Classification within 24 (-8/+12) hours post procedure (as read by the Core Lab and adjudicated by the CEC).
3. Device and Procedure Related Serious Adverse Events (PRSAE) within seven (7) days (-2/+3 days) or discharge, whichever is sooner.
4. Device and Procedure Related Serious Adverse Events (PRSAE).
5. Device-related Serious Adverse Device Effects.
6. Procedure-related mortality at seven (7) days (-2/+3 days) or discharge, whichever is sooner.
7. Stroke-related mortality at 90 days (±15 days) post-procedure.
8. All-cause mortality at 90 days (±15 days) post-procedure.
9. Neurological deterioration – defined by an increase of four (4) points or more on the NIHSS score, at the time of diagnosis compared to immediately before worsening within seven (7) days (-2/+3 days) or discharge, whichever is sooner.

The following safety information will be presented to the DMC for each treatment arm as part of the safety analysis:

10. Is there a difference in the incidence of all Adverse Events higher than anticipated in this population?
11. Is there a difference in the incidence of serious device-related neurological adverse events higher than anticipated in this population?

3.5. Additional Therapy

After three (3) passes with randomization assigned device, additional therapy if reperfusion is inadequate (i.e., less than eTICI 2b50), or additional therapy for improvement beyond eTICI 2b50 is permitted if determined to be in the best interest of the subject. Further treatment when reperfusion was not achieved (eTICI 0-2a) is termed “Additional Therapy for reperfusion failure,” and “Additional therapy” is used to denote further treatment when reperfusion with the randomized device was successful (eTICI 2b50-3) as shown in Figure 3-1. The operator is not required to complete three passes if earlier attempts suggest that further efforts would be futile or unsafe, or earlier attempts resulted in successful but incomplete reperfusion and the occlusion can no longer be treated within the Protocol (“valid exceptions”).

Use of any additional therapy prior to three (3) passes with the randomized device without a valid exception is a major protocol deviation, and these subjects will be excluded from the per protocol (PP) population analyses. Use of additional therapy after three (3) passes with the assigned device, or earlier with valid exception, is permitted and may be clinically warranted. the primary effectiveness endpoint will be derived 3 ways per Statistical Analysis section 8, with one analysis based on the observed results, independent of the use of additional therapies to retrieve the clot, the second where subjects who required Additional Therapy for reperfusion failure or additional off-label therapies to retrieve the clot are automatically treated as primary effectiveness endpoint failures, and the third where subjects who required Additional Therapy to retrieve the clot are automatically treated as primary effectiveness endpoint failures.

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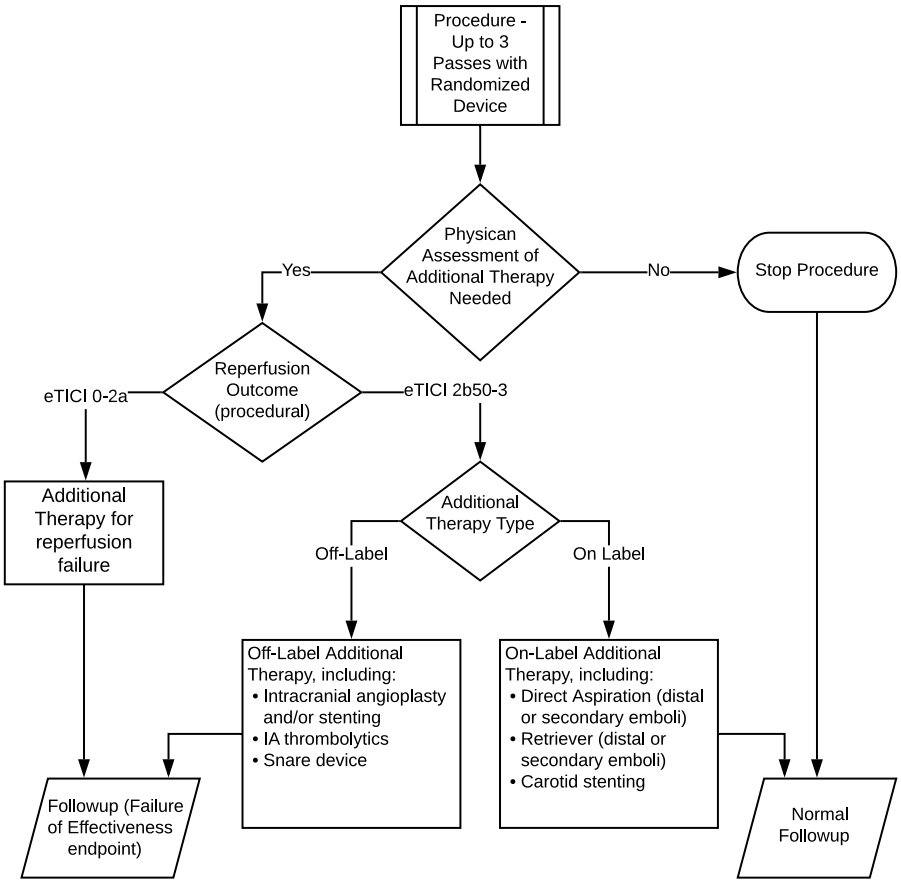
Figure 3-1: Additional Therapy Flowchart



3.6. Blinding

Each participating clinical site will have two (2) teams: an **unblinded team**, consisting of treating physicians and study coordinator who care for the patient/patient up to hospital discharge and clinical follow up visits, and a **blinded team**, with members certified in mRS assessment. The blinded team performs the mRS assessment at the 90-day visit, and the NIHSS assessment at the 24-hour and 7-day/discharge visits.

The Investigator will be blinded to treatment arm during screening, consent and enrollment, until point of randomization. At the point of randomization, the Investigator will be informed of which device is to be used in the procedure in order to safely perform the procedure according to the device IFU.

3.6.1. Patients

Randomized subjects will remain blinded to assigned treatment arm until the end of the study (as defined as 90-day follow-up). At the conclusion of the study all randomized subjects will be notified of their treatment arm.

3.6.2. Assessors

Assessors are blinded and certified. They are not the Investigator (e.g., treating physician) and while a part of the study team, will not have knowledge to subject's treatment arm.

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3.6.3. Blinded Assessments

The following are blinded assessments:

- NIHSS at 24 (-8/+12) hours
- NIHSS at seven (7) days (-2/+3 days) or discharge
- mRS at 90 days (± 15 days)

Imaging will be assessed by an independent Core Lab. The Core Lab reader will be blinded to the site assessments and clinical information during evaluation of the angiographic recanalization endpoints and intracranial hemorrhage.

4. Study Justification and Rationale

The purpose of this study is to assess whether the Envi™-SR, when used under routine clinical conditions, is at least as safe and effective as cleared predicate devices to treat patients presenting with acute ischemic stroke, specifically via evaluation of clinical outcomes at 90 - days (± 15 days). In the U.S. devices intended to be indicated to treat stroke are classified per 21 CFR 882.5600 as class II devices with special controls. One of these special controls is that clinical performance testing of the device must demonstrate the device performs as intended for use in the treatment of acute ischemic stroke. This requires the performance of a clinical trial.

Research in cases of acute stroke is challenging as the potential study cohort is very restricted. Hence efficient study design is important. In order to reduce risk as far as possible, enrollment will be reduced as far as possible while allowing for rigorous evaluation of the study research questions. An adaptive statistical design will be used with pre-defined stopping rules to most safely and efficiently evaluate the study research questions.

4.1. Measurement Scales

The following measurement scales will be used in the NV-001 Study:

- *mRS* – The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.
- *NIHSS* - The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.
- *eTICI*[19] Expanded Thrombolysis in Cerebral Infarction score. The thrombolysis in cerebral infraction (TICI) grading system is a tool for categorizing the degree of reperfusion during or after ischemic stroke. In neurointerventional radiology it is commonly used for patients post endovascular revascularization. The eTICI is a 7-point compilation of TICI grades that reflects all previously reported thresholds used to define reperfusion after endovascular stroke therapy. eTICI provides granularity in distinguishing the extent of reperfusion that is clinically meaningful.
- *Heidelberg Bleeding Classification* – The Heidelberg Bleeding Classification will be used to categorize intracranial hemorrhage into sICH or aICH based on both a pure

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radiological classification scheme and a combined radiological-symptomatic classification scheme. The Heidelberg Bleeding Classification was created to classify bleeding events after reperfusion therapy for reporting in AIS device trials. It provides a framework for classification of intracranial hemorrhage into classes, including hemorrhagic infarction (HI1, HI2), parenchymatous hematoma (PH1, PH2, rPH), intraventricular hemorrhage (IVH), subarachnoid hemorrhage (SAH), and subdural hemorrhage (SDH); and for classification of sICH vs. aICH.

4.2. Benefit / Risk Analysis

4.2.1. Context of the Proposed Investigation

This study intends to evaluate a novel mechanical thrombectomy device to treat patients suffering from acute ischemic stroke through a prospective, randomized pivotal study to provide an assessment of the safety and non-inferiority of the device.

4.2.2. Assessment of Risks of the Proposed Investigation

While mechanical thrombectomy has proven benefits in reducing disability in treatment of AIS, there are significant risks. Acute and long-term benefit to subjects that volunteer for enrollment in this trial are unknown. In addition to the currently known inherent risks associated with the procedures related to use of mechanical thrombectomy and any underlying conditions of the typical patient population, additional risks may arise in subjects randomized into the Envi™-SR arm. Reference Appendix C: Potential Adverse Events for a comprehensive catalogue of known Adverse Events associated with this treatment modality. This catalogue of potential Adverse Events is published in the Envi™-SR IFU and subjects will be made aware of potential risks via the informed consent process.

4.2.2.1. General Procedure Related Risks

The primary risk for subjects with large blockages in the brain is expansion of the core infarct or hemorrhage, which can cause increased neurological problems for the subject. The risks of poor neurological outcome are more common if the blockage is not removed. In cases of LVO, there is the potential for serious risks including death, neurological worsening, or serious bleeding into the brain. In previous studies of mechanical thrombectomy devices, the risk of death within 90 days of the stroke is in the range of 9% to 33%, neurological worsening in the range of 9% to 16%, and serious bleeding into the brain in the range of 0% to 7%, see Section 23.1: Typically Reported Serious Adverse Events (SAE). These ranges may overlap as subjects may develop serious bleeding in the brain leading to neurological worsening and/or death.

Additional potential risks of the treatment with either the Envi™-SR device or the Control Devices exist and are listed in Appendix C: Potential Adverse Events. These potential AEs may be the result of various parts of the disease or treatment over 90 days. These risks may result in additional tests, additional invasive procedures, blood transfusions, and permanent neurological deficits including paralysis, loss of vision, loss of speech, and memory loss, or death. These potential procedural risks are not anticipated to be significantly different than standard of care.

4.2.2.2. Procedural Imaging Risks

All subjects screened for the trial will undergo multi-modal diagnostic imaging and angiographic assessment to identify presence of hemorrhage, verify occlusion location, and to measure the core infarct volume. Risks associated with the baseline and follow-up imaging conducted as part of the trial are standard of care with mechanical thrombectomy treatment and are captured in Appendix C: Potential Adverse Events.

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There may be other angiograms performed as a part of standard stroke treatment with intervention. Arterial puncture can lead to bleeding that may be excessive and cause a blood clot that may require blood transfusion or surgical removal. The cerebral angiogram itself can cause problems including arterial perforation or dissection, embolism (air, thrombus, or other), aneurysm / pseudoaneurysm, or device failure and fracture.

Mild allergic reactions to angiographic contrast may occur. Severe reactions to angiographic contrast occur rarely. Subjects will be monitored for all possible allergic responses during and after the procedure. There are risks of kidney problems or kidney failure after receiving angiographic contrast during the angiogram and/or CT angiography. As with any subject having these procedures, kidney function and individual risk factors will be evaluated before the angiogram and subjects will receive sufficient fluids during the procedure to help avoid complications related to this.

During the angiographic procedure, if considered necessary by the treating physician for the subject's safety and comfort, a sedative and/or anesthesia with intubation may be administered. The risk of anesthetics and sedative agents include, but are not limited to, difficult breathing, hypotension, allergic reaction, and in rare instances life-threatening adverse events.

The CT scans, CT angiography, and cerebral angiography involve exposure to a small amount of radiation in addition to the usual x-ray studies done in stroke subjects. Although it has yet to be reported in studies for stroke treatments, this exposure may result in damage to the skin or hair due to the potential of focused exposure to x-rays. The radiation risk of the procedure is the same as conventional angiography and standard stroke treatment with intervention and does not involve an increased risk of radiation compared to mechanical thrombectomy with cleared devices. The risk of radiation is directly related to the length of the procedure, which is determined by the nature of the thrombosis being removed and the difficulty in accessing the affected anatomy.

There have been no ill effects reported from exposure to the magnetism or radio waves used in Magnetic Resonance Imaging (MRI). A known risk is magnetic attraction for objects containing ferrous metal. Therefore, subjects will be assessed for metal within the body (including certain dyes found in tattoos). Subjects with any uncertainty about potentially hazardous metal within their body will be excluded from participation in this study. Subjects with a history of claustrophobia or any related psychological manifestations that impair the ability to complete the scans required for this study may be excluded.

These potential imaging risks are not anticipated to be significantly different than standard of care.

4.2.2.3. Other Procedural Risks

Subjects who are pregnant or are breast feeding will be excluded. Subjects who become pregnant during this study will be required to contact their treating physician immediately upon confirmation of the pregnancy.

Routine collection of blood samples requires venipuncture. The risk of simple venipuncture commonly includes discomfort and/or bruising at the site of the puncture, and less commonly, infection at the site of the puncture, the formation of a small blood clot or swelling of the vein and surrounding tissue and bleeding from the puncture site.

These potential other procedural risks are not anticipated to be significantly different than standard of care.

4.2.2.4. Device Related Risks

Through the Envi™-SR risk assessment process conducted per EN ISO 14971:2012 and

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NeuroVasc Technologies, Inc. procedures, a multi-functional team identified risks associated with the design, manufacturing, and use of the device, and identified the characteristics related to its safety. The risks and safety characteristics have been evaluated with respect to the intended users, their level of education and training, and the intended purpose and use of the device.

Risk management and identification was conducted according to EN ISO 14971:2012 and product specific risk analyses, risk management files, and plans. Failure Mode and Effect Analysis (FMEA) was used to identify known risks associated with the development and use of the Envi™-SR and is a "bottoms up" approach to analyzing risk. The technique was applied to three separate categories: 1) the device design, 2) the process, and 3) the user interface. Potential hazards associated with the Envi™-SR were evaluated for their potential effects as well as their potential causes.

Following all mitigations to reduce risk under the risk management process, two (2) risks remained as undesirable:

1. The first is the risk of incorrect patient selection (leading to increased likelihood of futile recanalization or serious adverse events). This hazard is a consequence of the state of the art of stroke treatment based on current imaging and understanding of ischemia. While the rate of good functional outcome (mRS 0-2) has improved markedly with improvements in stroke systems of care and mechanical thrombectomy devices, there still exists significant uncertainty in patient selection. The intended patient population as defined in the NV-001 Study and indications for use of the Envi™-SR are consistent with current therapeutic guidelines and currently cleared Control Devices.[20] This risk is considered reduced as far as possible.
2. The second is the risk that the patient does not receive thrombolytic therapy. Similar to the risk of incorrect patient selection, this hazard relates to state of the art of stroke treatment, and not to mechanical thrombectomy devices. The use of thrombolytic treatment (typically IV t-PA) is a cognizant decision by the treating physician or medical team, not a "user error" based on the patient. The use of t-PA in the NV-001 Study follows established indications for use in the US and is considered reduced as far as possible.

As with all mechanical thrombectomy procedures, there is a possibility that serious Adverse Events may occur. Treatment with the Envi™-SR device may have unanticipated effects that no one knows about yet. In addition, risks due to subjects' individual reaction to the Envi™-SR device or its components, or to the control device could occur. Should any Adverse Events occur, they will be fully examined and monitored closely with special attention to UADEs as described in Section 12.

4.2.3. Risk Mitigation

4.2.3.1. Study/Procedure Related Risk Mitigation

Participating study sites will be assessed to ensure that the requirements and controls necessary for this trial are met prior to screening and enrolling subjects. Refer to Section 6.4 for these criteria.

Each subject or LAR will be required to review and sign an Informed Consent Form (ICF) prior to participation, see Section 5.2. The ICF will explain the intent and design of the trial, alternative treatment methods as well as the risks and potential benefits of participation.

An adaptive trial design is employed to limit study risk by stopping the trial for futility or early demonstration of non-inferiority. Stopping rules have been pre-specified.

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Independent oversight via the DMC, CEC, and Core Lab ensures that risks to participating subjects will be minimized. Safety monitoring of the data, consisting of individual event and aggregate data review, will be ongoing and conducted at a rate commensurate with subject enrollment in the trial. Specifically, the DMC will monitor adverse events and their occurrence rate throughout the study to advise on study continuation, modification or adjournment based on a review of a review of the comparative rates of Adverse Events of Special Interest. They will take into account in their decision making and recommendations the rates of procedure-related and device-related events in the control and treatment arms, refer to Section 12.3.

4.2.3.2. Device Related Risks Mitigation

Risk mitigation activities were conducted according to EN ISO 14971:2012 and product specific risk analyses, risk management files, and plans. Design, Process, and Use FMEAs identified hazards associated with the Envi™-SR design, manufacturing, and usage. Hazards were evaluated for potential hazardous situations, which were in turn evaluated for the potential to cause harm(s). The severity, likelihood, and detection (if applicable) of each risk sequence was evaluated for potential mitigation. Mitigations were implemented to reduce risk, and all risks identified were mitigated as far as possible. Residual risk levels have been deemed acceptable and appropriate for the intended use of the device.

The Envi™-SR is designed and manufactured in such a way that, when used under the conditions and for the purposes intended, it is not anticipated to compromise the clinical condition or the safety of patients or users. The risk management process has identified and reduced risks including user error as far as possible.

The risks and safety characteristics have been evaluated with respect to the intended users, their level of education and training, and the intended purpose and use of the device. Use risk will be minimized by selecting investigators experienced and skilled in mechanical thrombectomy and who have been trained in the NV-001 Study protocol per Section 13.

4.2.4. Assessment of Potential Benefits of the Proposed Investigation

The benefit of mechanical thrombectomy with stent retrievers is well established and has led to their adoption as the standard of care for a subset of patients experiencing AIS due to LVO in select patients up to 24 hours after stroke onset.[21]

The Envi™-SR method of action is similar to other mechanical thrombectomy retrievers currently available in the US, Europe and other regions around the world, including the Control Devices. In contrast to other retrievers, the Envi™-SR is designed with eccentrically mounted articulating segments. Testing with the Envi™ System retriever component in an *in vitro* model showed enhanced clot retrieval versus non-segmental designs when retrieved in tortuosity.[22] The Envi™ System retriever also underwent a First-in-human trial in Japan.[17] The Envi™-SR was based on the Envi™ System retriever component optimized for usage as the sole thrombectomy device. In pre-clinical testing in swine, the Envi™-SR demonstrated non-inferiority in various safety and effectiveness endpoints. Based on the similarity in method of action, *in vitro* and *in vivo* pre-clinical testing, clinical evaluation, and early clinical experience, the Envi™-SR is expected to be non-inferior to currently available stent retrievers.

Clinical effectiveness of the Envi™-SR has not been established and acute and long-term benefit to subjects that volunteer for enrollment in this trial are unknown.

4.2.5. Consideration of Patient Preference Information

The Envi™-SR and Control Devices are prescription-only devices used in emergency procedures and are not expected to have significant patient preference considerations.

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4.2.6. Assessment of Uncertainty

As the benefit of mechanical thrombectomy with stent retrievers in the treatment of AIS has been well established, the uncertainty of benefit and risk of this trial is predominantly regarding the Envi™-SR device. In the absence of a pivotal clinical trial, the safety and effectiveness of the Envi™-SR is uncertain, and subjects may receive no direct benefit from study participation.

Non-clinical bench testing has consistently demonstrated the ability of the Envi™-SR and the previous generation Envi™ System retriever to meet product specifications and user needs. These data have supported the CE mark of the Envi™-SR and the previous generation Envi™ System retriever. Pre-clinical GLP animal data is consistent with bench testing data and supports the acceptability of risks and potential benefits.

Limited clinical experience on the Envi™ (aka Versi) Retriever in Japan and Europe has provided additional validation in humans supporting the acceptability of the risk profile, which reduces the uncertainty of risks and potential benefit. Limited commercial experience with the Envi™-SR has provided no indication of unanticipated risks and further reduces uncertainty. This study is designed as a prospective, multinational, randomized, parallel group-controlled, blinded, non-inferiority study in order to reduce uncertainty and establish the safety and effectiveness of the Envi™-SR.

4.2.7. Risk Benefit Conclusion

The undesirable residual risks noted are related to the state of the art of stroke treatment and not to the Envi™-SR specifically, and have been mitigated as far as possible in the NV-001 Study. The benefits of mechanical thrombectomy with the Control Devices have been demonstrated by multiple prospective randomized trials to outweigh the risks of treatment in the indicated patient population. The Envi™-SR is expected to provide a similar benefit / risk profile.

The Envi™-SR may offer benefits in revascularization when retrieved in neurovascular tortuosity, which may be predictive of better clinical outcomes. Despite inherent risks in treating patients who present with AIS, available information indicates the Envi™-SR has a risk/benefit profile not inferior to cleared devices, and when monitored and conducted per the protocol the potential benefits of treatment with the Envi™-SR justifies the risks.

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5. Subject Selection

5.1. Enrollment

5.1.1. Enrolled Population

All consecutive patients with a signed Informed Consent Form (ICF) will be considered part of the enrolled population.

5.1.1.1. Enrolled Screen Failures

Subjects who are consented but do not meet all inclusion/exclusion criteria, are not randomized and device placement is not attempted, will be classified as enrolled screen failures. All patients that are consented are enrolled subjects and will count toward the total allowed study enrollment even if they are determined to be screen failures after consent.

5.1.2. Intention to Treat (ITT) Population

A subject that is enrolled and randomized to a treatment arm is considered part of the ITT population. The ITT population will form the basis for the primary analysis dataset, independent of the subject actually receiving the randomized device.

5.1.3. Per Protocol Population

An enrolled subject that meets all inclusion/exclusion criteria, receives the randomized device, and has no major protocol deviations that significantly change the intent or outcome of the protocol for the subject will be considered part of the Per Protocol (PP) population.

5.1.4. As-Treated Population

An enrolled subject that receives treatment with either the Envi™-SR or a Control Device after consent and randomization will be analyzed according to the treatment received (regardless of randomization) in the As-Treated population analysis.

5.2. Informed Consent

Prior to admission to the study, a patient Informed Consent Form (ICF) will be given to each prospective subject or their LAR (as defined by the local IRB/EC/REB), including an explanation of the study, duration, explanation of medical record access and patient anonymity, and how their coded data may be transferred, used for publications or in submissions for reimbursement support. The ICF will contain language that is non-technical and understandable (translated ICFs will be provided where applicable) to the patient or his/her legal representative. The treatment occurs in an acute emergency situation, so locally required ICF procedures may apply and will be complied with.

Each potential subject will be provided with written and verbal information regarding the nature of the study in an understandable manner. Adequate time will be allowed for the subject to consider participation in the clinical study. Signed, written consent will be obtained for each subject prior to data collection and entry into the study. Any coercion or undue influence of potential subjects to participate must be avoided, and the subject's legal rights should not be waived. The Investigator or an appropriately designated member of the study staff shall co-sign the consent form, indicating they believe the subject has understood the nature and risks of the study and, in their estimation, the subject clearly understands the scope of the consent. The Investigator must inform subjects that they are in a controlled clinical study, apprise them of their rights as set forth in the ICF, and document the discussion in their medical record.

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If the subject is not able to give his/her informed consent to participate in the study, a LAR can sign the ICF for the subject if this is approved by the IRB/EC/REB.

Short form informed consent, electronic consent, or appropriate teleconsent platforms may be utilized if approved by the IRB/EC/REB. Each institution must follow their institutional IRB/EC/REB policy for obtaining informed consent. If the short form, or alternative (e.g., teleconsent) informed consent is used, the summary must include all the basic elements of informed consent (21 CFR 50.25; ICH E6 4.8.10).

The procedure around how the informed consent is collected will be recorded in each subjects' medical record. The signed ICFs will be retained by the Investigators and made available (for review only) to the study monitor/auditor on request.

Each site will maintain a log of all screened patients detailing the reasons for any subsequent patient exclusions or non-participation in the study.

5.3. Subject Withdrawals

Participation in this IDE Study is voluntary, and the subject may withdraw at any time. All ITT subjects will be included in data analysis, unless they withdraw permission for their data to be used. The Sponsor will retain and continue to use any data collected prior to the withdrawal of informed consent, unless specified by the subject or their LAR.

In the event the subject chooses to withdraw, he/she will be instructed to contact the Investigator immediately. Withdrawal from the investigation will not affect the subject's follow-up care. The subject will be informed of any significant information regarding new findings that may develop during the course of the research study that may relate to his or her willingness to continue participation as a study subject.

Subjects will participate in their routine follow-up and allow this data to be gathered or their participation in the study will be prematurely terminated. If their participation is terminated, any of their data which has been already gathered will continue to be included. The completion of a subject's participation in the study or early departure from the study must be fully documented in the subject's study progress notes.

Subjects will be considered exited (i.e., discontinued) from the study if any of the following occur:

1. If, during the conduct of the study, a subject dies, all available information should be obtained, and an appointed NeuroVasc Technologies representative/ study monitor should be notified no more than 24 hours from study staff becoming aware of the event.
    a. If a subject's death occurs while in the hospital, submit a copy of the physician's death summary report. If an autopsy is performed, submit a copy of the autopsy report, as well. If a subject's death occurs outside of the study site, obtain all information related to the death and submit the investigator's summary of the events associated with the death.
2. Subject voluntarily withdraws from the study. A subject may withdraw consent from study participation at any time.
3. Subject does not meet inclusion / exclusion criteria after consent but prior to randomization (enrolled screen failure). The subject will be followed for a minimum of 48 hours or until discharge, whichever is earlier, and exited from the study.
4. Subject withdrawn from the study by the investigator. An investigator may withdraw an enrolled subject from the study for the following reasons:

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a. Major Protocol Deviation:

   Should a subject be enrolled but later determined ineligible based on previously unavailable source documentation or due to a deviation in following the protocol at the study site, this subject will be considered a major protocol deviation. A comparison of the incidence of patients who have a major protocol deviation will be performed between the randomized treatment groups. A 2-tailed Fisher's exact test will be used to determine if the proportion of patients with deviations differences significantly between the 2 treatments.

   All protocol deviations should be documented by the study monitor appointed by NeuroVasc Technologies.

b. Subject is Lost to Follow-up

c. Investigator's discretion

5.4. Subjects Lost to Follow-up

If a subject fails to return for the 90-day follow-up visit, five (5) calls to their last known contact number will be done within two (2) weeks. If those attempts are unsuccessful, a certified letter will be sent to their most current mailing address, reminding them of their study obligations. When all reasonable attempts to locate the subject have been exhausted, including contacting the subject's general practitioner and additional documented contacts (e.g., family members or trusted individuals), the subject will be considered lost to follow-up. Documentation is required for all attempts to locate the subject.

The primary method for analysis will use multiple imputation to address missing data. As a sensitivity analysis for the primary endpoint, the baseline value will be imputed for the 90-day result, functionally resulting in no change from baseline in the mRS score. A separate sensitivity analysis will be conducted imputing the worst mRS score at 90-days recorded for a patient within their respective treatment group. A sensitivity analysis of the primary safety endpoint will also be conducted. Additional details are provided in Section 8 of this protocol and the SAP.

6. Study Design

The study is designed as a prospective, multinational, randomized, parallel group-controlled, blinded, non-inferiority study to evaluate the performance of the Envi™-SR against devices currently on the market for the same indication.

6.1. Allocation

Subjects who consent and meet the inclusion/exclusion criteria will be randomized to one of the following two Treatment Arms: Envi™-SR or Control Device. Subjects will be randomized 1:1 to each Treatment Arm.

6.1.1. Intervention Model

Subjects will be randomized in parallel assignment.

6.2. Control Device

Currently there are two FDA-cleared stent retriever families with indications for treatment of acute ischemic stroke: the Stryker Neurovascular Trevo® family and the ev3 Neurovascular/Medtronic Solitaire™ family. The Trevo® family consists of the Trevo ProVue®

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Retriever, Trevo® XP ProVue Retriever, and Trevo NXT™ ProVue Retriever. The Solitaire™ Revascularization Device family includes the following: Solitaire™ Platinum, Solitaire™ 2, Solitaire™ 4, and Solitaire™ X.

All Control Devices used must be used within their Indications for Use.

The proposed Envi™-SR indications for use match the Trevo® family of devices. Hence the time from stroke onset to usage (up to 24 hours) and imaging criteria are identical and the inclusion/exclusion criteria for the NV-001 study align with this indicated patient population.

The Solitaire™ Revascularization Device family has similar indications for use, however the indicated time from stroke onset to usage is up to 16 hours from onset or time last seen well (TLSW). Therefore, in the case of a subject randomized to the Control Device at 16 to 24 hours from onset or TLSW, only the Trevo® family will be permitted to be used.

The devices in Table 6.1 are currently cleared and may be used as the Control Device.

Table 6.1: Control Devices for ENVI RCT

Family	Product	Size
Stryker Neurovascular Trevo®	Trevo ProVue® Retriever	4x20mm
	Trevo® XP ProVue Retriever	3x20mm
		4x20mm
		4x30mm
		6x25mm
ev3 Neurovascular/ Medtronic Solitaire™	Solitaire™ Platinum Revascularization Device	4x20mm
		4x40mm
		6x20mm
		6x24mm
		6x40mm
	Solitaire™ X Revascularization Device	4x20mm
		4x40mm
		6x20mm
		6x24mm
		6x40mm
	Solitaire™ 2 Revascularization Device	4x15mm
		4x20mm
		4x40mm
		6x20mm
		6x30mm

6.3. Enrollment Design

The study is planned to include up to 448 subjects.

This study will be conducted in up to 30 centers, located in the United States (U.S.), Canada and European Union (EU). The study will be registered and results will be reported to the U.S. database maintained by the United States National Institutes of Health (NIH) on the United States National Library of Medicine's ("NLM") website www.clinicaltrials.gov under Title VIII of the Food and Drug Administration Act of 2007 ("FDAAA"). The expected duration of subject enrollment is approximately 90 days (± 15 days). Subjects will be followed through 90 days (± 15 days) with assessments at hospital discharge and 90 days (± 15 days).

An independent Core Lab will confirm occlusion as recorded on baseline CTA/MRA imaging, and score reperfusion. In addition, the independent Core Lab will assess 24 hours (-8/+12 hours) post treatment images for evidence of ICH. An independent CEC will adjudicate study safety endpoints. An independent DMC will evaluate all adverse events throughout the study and will monitor subject safety. The CEC and DMC will perform their duties in accordance with

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this protocol, the DMC Charter, and the CEC Charter associated with this study.

6.4. Site Selection

The sponsor or a representative of the sponsor will assess each potential site to ensure the Investigator and their staff has the facilities and expertise required for the study. Sites will be selected based upon a site qualification assessment considering appropriate facilities, and the qualifications of the Investigator(s). Individual Investigators will be evaluated by the sponsor based on experience with the intended procedure(s), and ability to conduct the study according to the study protocol.

Investigators and sites will be selected based upon the following factors:

- Previous experience with clinical research and mechanical thrombectomy procedures.
- Experience in conducting randomized, controlled clinical studies.
- Willingness to observe confidentiality at all times.
- Currently treating subjects who meet the inclusion/exclusion criteria.
- Ability to enroll an adequate number of subjects.
- Ability to perform required clinical testing, including angiography, CT, and/or MRI.
- Ability and willingness to provide the sponsor's representatives, FDA and local regulatory authorities access to the hospital records, study files, and subject files as they pertain to the study.
- Willingness to participate, including compliance with all aspects of the study.
- Adequate staffing to conduct the study. This includes:
    - Principal Investigator (PI): Responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs eCRFs indicating documents are accurate and complete.
    - Sub/Co-Investigator(s) (Sub-I/Co-I): Responsible for study activities in coordination with PI and in accordance with the investigational plan. Assume the responsibility of the PI should the PI resign from the study. A site is not required to have a co-investigator.
    - Study Coordinator: Assists PI with study activities as delegated by the PI, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing eCRFs to the sponsor in a timely manner.
    - Blinded and Certified Assessor: Responsible for clinical evaluations at 90-day follow-up

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6.5. Inclusion Criteria

Study subjects must meet ALL of the inclusion criteria listed below:

1) Clinical signs consistent with acute ischemic stroke
2) Pre-stroke Modified Rankin Score ≤ 2
3) Age 18 years and no upper limit (patient must be 18 years old at time of consent.)
4) NIHSS ≥ 6 at the time of randomization
5) Subject is able to start treatment (defined as time of arterial puncture) within 24 hours of stroke onset or last known well and within 90 minutes from last baseline CT/ MRI.
6) Imaging: For strokes in the anterior circulation the following imaging criteria should also be met:
   a) If stroke onset (as defined by the time the patient was last seen at baseline) is within 6 hours: Baseline ASPECTS ≥6 on non-contrast CT (NCCT) or DWI-MRI;
   b) If stroke onset is within 6-24 hours, advanced imaging with either CT perfusion or DWI-MRI is required. Baseline infarct volume must be ≤50cc for patients under 80 years old and ≤20cc for patients 80 years or older.
7) Location: Angiographic confirmation of an occlusion of an ICA (including T or L occlusions), M1 or M2 MCA with eTICI flow of zero (0) – one (1).
8) Patients for whom IV t-PA is indicated, are treated with IV t-PA without delay.
9) IV t-PA, if used, is initiated within three (3) hours of stroke onset (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the subject has received/is receiving the correct IV t-PA dose for the estimated weight.
10) Consent: The patient or the patient's LAR has signed and dated an Informed Consent Form.
11) Will comply with protocol follow-up schedule.
12) Patient was ambulatory prior to stroke, i.e. able to walk without another person's assistance.

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6.6. Exclusion Criteria

Subjects must NOT meet ANY of the exclusion criteria listed below:

1) Life expectancy likely less than six (6) months.
2) Females who are pregnant or breastfeeding.
3) Known history of severe allergy (more than rash) to contrast medium that cannot be medically controlled.
4) Suspicion of renal failure (Renal failure as defined by a serum creatinine >3.0 mg/dL (264 µmol/L) or Glomerular Filtration Rate (eGFR) <30).
5) Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg) NOTE: If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled.
6) Currently participating in another interventional (drug, device, etc.) research project that may confound the results of this study.
7) Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency. (A subject without history or suspicion of coagulopathy does not require INR or prothrombin time lab results to be available prior to enrollment.)
8) Known history of platelet count <100,000/µL.
9) Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol).
10) Subjects with occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation).
11) CT or MR evidence of hemorrhage.
12) Seizures at stroke onset.
13) Suspicion of aortic dissection.
14) Patients with known hypersensitivity to nickel-titanium.
15) Evidence of dissection in the extra or intracranial cerebral arteries.
16) Stenosis, or any occlusion, in a proximal vessel that requires treatment or prevents access to the site of occlusion.
17) Presumed septic embolus, suspicion of bacterial endocarditis, or other serious infection.
18) Suspected cerebral vasculitis based on medical history and CTA/Magnetic Resonance Angiogram (MRA).
19) Excessive vascular access tortuosity that will likely prevent endovascular access.
20) Baseline CT or Magnetic Resonance Imaging (MRI) showing intracranial tumor (except asymptomatic small meningiomas less than three (3) cm).
21) Significant mass effect with midline shift
22) Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies three months prior to use of treatment device
23) Unlikely to be available for 90-day (± 15 days) follow-up (e.g. no fixed home address, visitor from overseas).
24) Rapid neurological improvement prior to study enrollment suggesting resolution of signs/symptoms of stroke such as a decrease that leads to a NIHSS below the study cut-off of six (6).
25) Patient has suffered a hemorrhagic or ischemic stroke or TIA within the last three (3) months.
26) Patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, mRS score at baseline must be ≤ 2. This excludes patients who are severely demented, require constant assistance in a nursing home type setting or who live at home but are not fully independent in activities of daily living (toileting, dressing, eating, cooking and preparing meals, etc.).
27) Known cancer with metastases.
28) Subject currently uses or has a recent history of illicit drug(s), which includes marijuana.
29) Recent past history (within three (3) months) or clinical presentation of intracranial

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hemorrhage (ICH), subarachnoid hemorrhage (SAH), ruptured arteriovenous malformation (AVM) or ruptured aneurysm.

30) The patient is in a coma.

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6.7. Device Training

Physicians will be trained in the use of the Envi™-SR before any patient procedures. To further assure optimal device use, participating investigators will be trained by the sponsor on proper device selection and use and given ample opportunity to fully address any technical questions that may be present. Participating centers will be selected based on volume of potential cases, research experience of study team, professional qualifications, and extent of experience with the endovascular treatment of stroke. The sponsor will provide hands-on flow model testing with each investigator delegated for device use / deployment prior to the site being released to enroll patients to the study.

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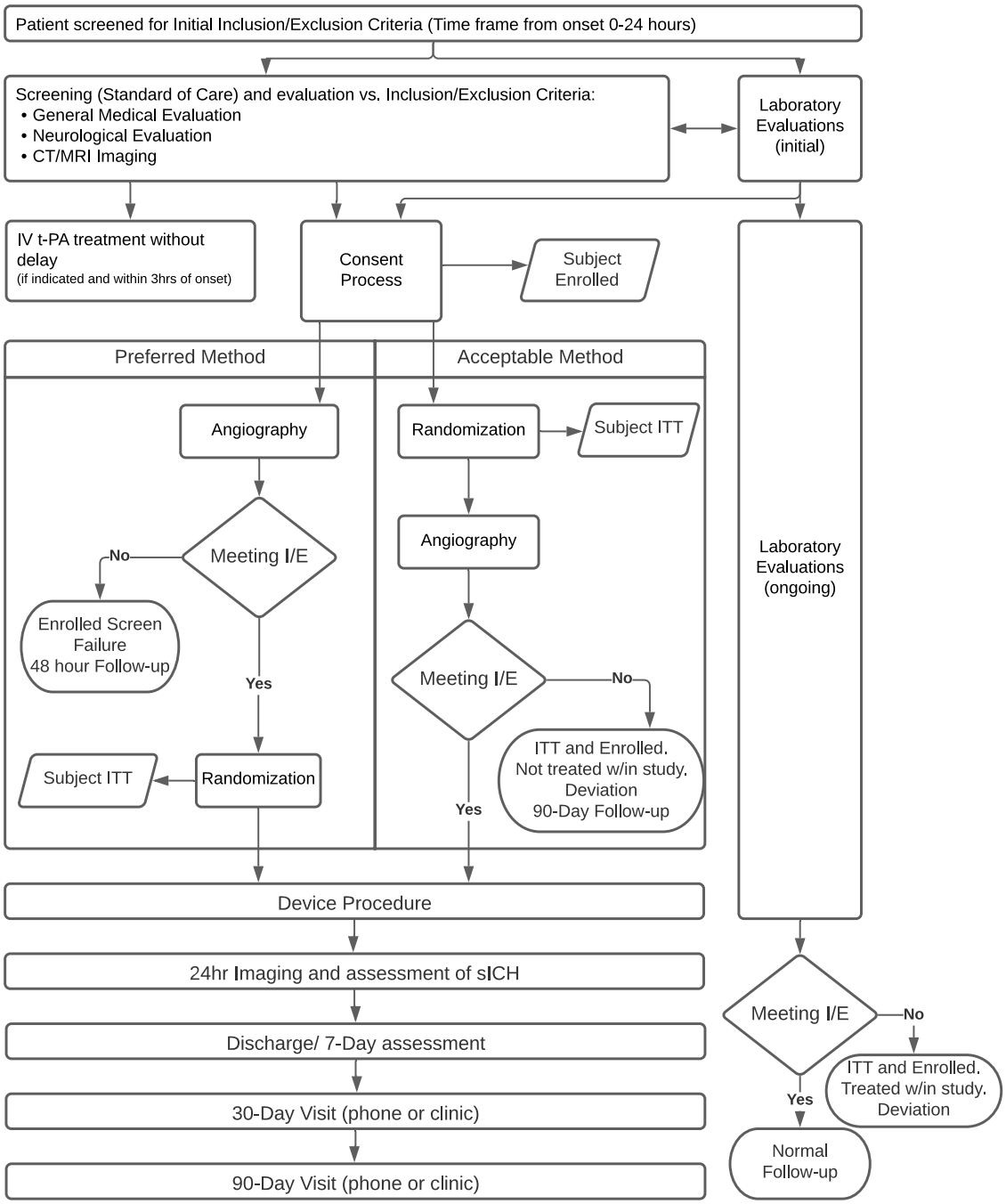
6.8. Study Procedures

6.8.1. Study Flow

Subjects presenting with acute ischemic stroke will be evaluated by the physician, in accordance with their institutional practice, to establish an appropriate treatment plan based on the Subject's medical condition and available diagnostic screening procedures prior to recruitment in the NV-001 Study. A representative overview of the study flow is shown in Figure 6-1.

Figure 6-1: Study Flow: Patient is in study from time informed consent is obtained



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6.8.2. Screening

Subjects will be screened against the study inclusion/exclusion criteria to determine their initial eligibility. A member of the research team (hospital/institution personnel assigned to the NV-001 Study should review their eligibility. All subjects screened will be documented on the Screening/Enrollment log, including the reason for non-participation for subjects who do not enroll.

6.8.2.1. General Medical Evaluation

- A physical examination and medical history.
- Blood pressure and pulse prior to randomization.
- Concomitant medication at baseline

6.8.2.2. Laboratory Evaluation

Blood and/or urine specimens for the following laboratory studies:

- Pregnancy test – (for female patients with childbearing potential. Pregnancy test to be conducted with urine or serum sample, per institutional standard of care)
- Hemoglobin, and platelet count.
- Coagulation parameters: activated partial thromboplastin time (aPPT) and international normalized ratio.
- Kidney function: creatinine or eGFR
- Serum glucose.

6.8.2.3. Neurologic Evaluation

Screening NIHSS should be recorded as performed. At screening, a pre-stroke mRS will be obtained from the subject or the subject's caretaker.

6.8.2.4. Computed tomography or magnetic resonance imaging

CT or MRI obtained prior to study enrollment will be used for baseline assessment.

6.8.2.5. Baseline Angiography

Baseline angiogram is preferred to be obtained prior to randomization to assess inclusion/exclusion criteria as well as to assess clot location. It is acceptable to perform baseline angiography after randomization.

6.8.2.6. Screen Failure Prior to Randomization – Follow-up

Subjects that have been enrolled (i.e., consented) but not randomized will be followed for a minimum of 48 hours or until discharge, whichever is earlier, to monitor subject safety. The reason for screen failure and follow-up will be captured in the *Early Exit Due to Screen Failure* eCRF.

6.8.2.7. Randomization method

Subjects meeting the enrollment criteria, including angiographic criteria, will be randomly assigned to a treatment group in a 1:1 ratio, Envi™-SR to Control device. Randomization will define the ITT population and the assignment will determine the treatment group for the ITT analysis. Randomization assignments will be allocated through an electronic system, each initiated study site will be issued their own unique password, at least one password per site, and multiple passwords will be assigned if more than one person is randomizing subjects. Thus, Investigators can quickly determine the randomization assignment and the treatment assignment will be documented for monitoring. Deviations in treatment from the randomized

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assignment will be recorded in the *Protocol Deviation* eCRF as a protocol deviation.

6.8.2.8. Screen Failure After Randomization – Follow-up

Subjects that have been enrolled and randomized but subsequently are found to not meet inclusion / exclusion criteria will be recorded in the Deviation eCRF as a protocol deviation. These subjects are a part of the ITT population regardless of treatment and will be followed per standard study procedures.

6.8.3. Procedure

- Using standard interventional techniques access the arterial system and using angiography, determine the location of the occluded vessel.
- Using standard angiographic technique, navigate a compatible guide / intermediate catheter, then navigate a compatible microcatheter and guidewire to the thrombus location.
    - It is recommended to use the Retriever with a proximal flow regulation device, such as a balloon guide catheter.
    - If a distal guide / intermediate catheter is planned to be used, it is recommended to use a balloon guide catheter or long sheath for support. These can also facilitate clot retrieval if the clot and Retriever cannot be pulled into a distal guide / intermediate catheter.
- Advance an appropriate Guide Catheter, Sheath or Balloon Guide Catheter as close to the occlusion as possible. Connect a rotating hemostasis valve (RHV) to the proximal end of this catheter and connect to a continuous flush system.
- Select an appropriate microcatheter. Connect an RHV to the proximal end of the microcatheter and connect to a continuous flush system.
- With the aid of a suitable guidewire, if needed, and using standard catheterization techniques and fluoroscopic guidance, advance the microcatheter up to and across the occlusion so that the distal end of the microcatheter is positioned distal of the occlusion.
- Remove the guidewire from the microcatheter and, if desired, gently infuse contrast media through the microcatheter to visualize the distal end of the occlusion.
- Select the appropriate Envi™-SR or Control Device based on target vessel anatomy. Follow Instructions for Use provided in device packaging for positioning, deployment and retrieval and cleaning and re-use of device.
- Do not attempt more than three (3) retrieval attempts with assigned device in the same vessel.
- Note: Direct aspiration prior to 3 passes with randomized device is not allowed per protocol unless there is a valid exception per Section 3.5.

6.8.3.1. Procedural Angiography

- Per Pass angiogram(s)
    - Obtained immediately after completion of each and every Envi™-SR, Control Device, and/or additional therapy pass
- Post-assigned device use angiogram
    - After the final assigned device use
- Post-procedure angiogram after all treatments (if different than post-assigned device use angiogram)
    - The final post procedure angiogram should comprise a full A-P lateral image.

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6.8.4. 24 Hour (-8/+12 hrs.) Follow-up

The 24 hour (-8/+12) hour follow-up visit includes:

- An NIHSS examination, assessed by blinded and certified study team member
- CT or MRI imaging.
- Record any adverse events which occur after the procedure and up to the time of the 24-hour examination.

CT or MRI will be obtained to assess any presence of hemorrhage. It is preferred, but not required, that whether CT or MRI is taken at baseline, to make direct comparison easier, the same imaging modality is obtained at follow-up.

This visit is not applicable for enrolled screen failure subjects.

6.8.5. 7 Day (-2/+3 days) or discharge Follow-up

The 7 days (-2/+3 days) or discharge (whichever is sooner) follow-up visit includes:

- An NIHSS examination, assessed by blinded and certified study team member
- Abbreviated Physical Examination
- Concomitant medications
- Record any adverse events which occur after the 24-hour time point and up to the time of the 7 days (-2/+3 days) or discharge.

6.8.6. 30 Day (±14 days) Follow-up

The 30 days (±14 days) follow-up visit includes:

- A mRS per the RFA-A
- Abbreviated Physical Examination
- Concomitant medications
- Record any adverse events which occur after the 7 days (-2/+3 days) or discharge.

In-person assessment is preferred, however telemedicine assessment is acceptable if clinical visit not possible.

6.8.7. 90 Day (±15 days) Follow-up

The 90 Day (±15 days) follow-up visit includes:

- A mRS, assessed by blinded and certified study team member per the RFA-A
- Record any adverse events which occur after the 30 days (±14 days) or discharge time point and up to the time of the 90-day (±15 days) examination.

In-person assessment is preferred, however telemedicine assessment is acceptable if clinical visit not possible.

6.8.8. Unscheduled Visit Follow-up

The unscheduled visit includes:

- mRS, assessed by blinded and certified study team member per the RFA-A (if possible)
- Concomitant medications
- Record any adverse events which occur since last study visit and up to the time of the 90-day examination.

In-person assessment is preferred, however telemedicine assessment is acceptable if clinical visit not possible.

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6.8.9. Completion

Subjects who successfully complete the 90-day visit will be considered as successfully completing the study.

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6.8.10. Schedule of Events Summary Table

Table 6.2: Study Visits and Assessments							
Study Requirement	**Screening**	**Procedure**	**Post Procedure**				
	Within 24 hrs. of stroke onset	Time 0	24 Hours (-8/+12)	7 Day (-2/+3) or Discharge[5]	30 Day (±14) [9]	90 Day (±15) [9]	Unscheduled
Informed consent	X[1]						
Pregnancy test	X[2]						
NIHSS Score	X		X[8]	X[8]			
Modified Rankin Scale (mRS)	X [3]				X	X[8]	X
Medical history	X						
Physical examination	X			X[10]			
Blood Pressure and Pulse	X						
Assess/confirm study eligibility	X						
Cerebral Imaging (CT or MRI)	X[12]		X[12]				
Hemoglobin and Platelet Count	X[11]						
Serum Glucose	X[11]						
Serum Creatinine or eGFR	X[11]						
INR, aPTT	X[11]						
Angiography	X [6]	X [7]					
Randomization		X					
Mechanical thrombectomy		X					
Concomitant medications	X			X	X	X	X
Record adverse events[4]	X	X	X	X	X	X	X

(1) Patient or Legally Authorized Representative must sign informed consent prior to screening specific tests which are beyond the local standard of care.
(2) Per institutional standard of care, for females of childbearing potential, subjects must have a documented negative pregnancy test prior to device insertion except in the case of local regulations and ethic committee approvals requiring consent post the emergency situation.
(3) Pre-ictus (Latin for Stroke)
(4) Record all adverse events from the time of signature of the ICF.
(5) To be performed at 7 days (-2/+3 days) or at discharge (whichever occurs first).
(6) Perform baseline to verify the angiographic inclusion/exclusion criteria are met.
(7) Perform angiography after every device pass, and after each additional therapy device pass. Obtain a final angiogram at the end of the interventional procedure.
(8) Assessed by blinded and certified study team member, mRS per the RFA-A.
(9) Visit may be conducted by telemedicine if clinical visit not possible.
(10) Physical exam to be conducted per institution standard of care
(11) If required per local standard of care or inclusion/exclusion criteria
(12) Per institutional standard of care. MRI with DWI is preferred, CT is acceptable. It is preferred that the same imaging modality is used at 24 hour timepoint as at baseline (CT or MRI) to make direct comparison easier.

6.9. Imaging Core Laboratory

The objective of the Imaging Core Lab (Core Lab) is to provide an unbiased assessment of the CT, MRI, and angiographic imaging from the study sites. Data provided by the Core Lab will serve as the 'gold standard' and will be used for data analysis. Each angiogram will be read by an experienced Core Lab reader.

The following imaging and angiography variables will be extracted by the Core Lab based on direct prior experience with these measures and scales, using the published definitions and standards:

Pre-Baseline (Outside Hospital, if available):

- ASPECTS
- Hemorrhage

Baseline:

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- ASPECTS
- Ischemic core volume – post hoc DWI or CTP rCBF<30% volumes when available
- Tmax > 6 sec volume (if CTP or PWI available)
- Hemorrhage
- Baseline occlusive lesion location
- Presence of occlusions in more than one territory
- CTA collateral score – based on availability (post hoc)

Procedure:

- Presence of stenosis proximal to arterial occlusive lesion
- Arterial occlusive lesion
- Collateral flow grade - ASITN
- eTICI on each device pass
- Distal emboli
- Emboli to new territories
- Evidence of vessel injury

Post-Procedure (24 hour):

- ASPECTS
- Final infarct volume post hoc DWI or CTP rCBF<30% volumes when available
- Hemorrhage (Heidelberg)

Neurological Deterioration or Course Post-Procedure:

- ASPECTS
- Relevant imaging findings and measures, based on availability

The Core Lab will perform an unbiased and blinded assessment of sICH for the primary safety endpoint and hemorrhage related to other safety endpoints. The Core Lab will also have the responsibility to evaluate the 24- hour post-procedure CT/MRI examinations to detect and assess new hemorrhages. Hemorrhages will be radiologically classified as described in Appendix A.

The Core Lab will perform an unbiased and blinded evaluation of the rate of revascularization defined by eTICI scores based on angiographic imaging from the study sites for relevant secondary endpoints.

The Imaging Core Lab is fully compliant with Health Insurance Portability and Accountability Act (HIPAA), the privacy rules and regulations set forth by the U.S. Department of Commerce and the European Commission with regard to the European Data Protection Directive (Directive 95/46/EC), as well as various industry data security standards, such as the Statement on Standards for Attestation Engagements (SSAE 16). Case Report Forms will be completed and provided to the Core Lab, via an electronic data capture system or other designated means.

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6.10. Subjects

The study population for this clinical study will be comprised of adult patients who have been diagnosed with acute thrombotic or thromboembolic stroke with onset of symptoms less than 24 hours prior to enrollment. In addition, these patients must satisfy all inclusion and exclusion criteria.

6.10.1. Use of OUS Data

The clinical practice in Europe and Canada for treatment of acute ischemic stroke is very similar to that in the U.S., endovascular device handling and use is identical, and post treatment follow up practices are very similar. These are the non-patient-dependent factors that most affect outcome. The use of IV t-PA is specified per protocol to be used only within three (3) hours of stroke onset for this study. Data generated from different geographies will be evaluated for poolability based on the statistical criteria described in Section 8 and the SAP.

Data collected outside the U.S. will be collected according to GCP as defined in this protocol and other study documents. Human subjects will be protected according to International Conference of Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), ISO 14155:2011, the Declaration of Helsinki, and the pertinent individual country laws/regulations. This study will be conducted in compliance with applicable requirements in the Protection of Human Subjects regulations in 21 CFR part 50, the Institutional Review Boards regulations in 21 CFR part 56, and the Investigational Device Exemptions regulations in 21 CFR part 812.[23]

6.10.2. Clinical Practice

Either CT or MRI are appropriate for screening stroke. Actual endovascular treatment in the US, Canada and Europe occurs in a catheterization laboratory (also known as Cath Lab). Cath lab practices and procedures and follow up care for AIS patients do not differ in a manner that could affect outcome measured with mRS

In both the US, Canada and Europe, patients experiencing an acute ischemic stroke receive lytic IV t-PA (if they are suitable candidates); if this is not effective then they are treated endovascularly with a stent retriever. The investigator may wait 60 minutes to see if the lytics achieve revascularization before mechanical thrombectomy or may initiate revascularization within 60 minutes.

While in the United States, Canada and Europe lytic therapy is recommended for patients meeting the European cooperative acute stroke study (ECASS) inclusion/exclusion criteria between the 0-4.5 hour from stroke onset, IV t-PA is not FDA approved for use after three (3) hours from stroke onset. In this study, IV t-PA usage will be on-label for the US indication and will not be administered after three (3) hours from stroke onset in study Subjects.

There are no other population or location specific treatment differences present between the patient treatment in the U.S. and those in Canada and in Europe which could reasonably be suggested to influence results.

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7. Assessment of Safety

The following assessment criteria will be used to evaluate the safety endpoint of the study.

7.1. Cerebral CT or MR Imaging

This study will collect imaging data in line with routine practice as follows:

- Pre-procedure CT/ MRI
- 24-hour (-8/+12) CT/ MRI

All imaging should be in line with standard of care. No extra imaging should be performed for the purpose of the study. No patient should be exposed to extra radiation as a result of participation. It is preferred that the same imaging modality is used at 24 hour timepoint as at baseline (CT or MRI) to make direct comparison easier. MRI DWI is preferred, CT is acceptable.

Any other imaging performed (for example as a result of clinical deterioration) will also be provided.

In the event of abrupt neurologic deterioration or when deemed necessary by the investigator, an emergency CT or an MR imaging evaluation should be performed. An immediate evaluation of the presence/absence of hemorrhage, edema, and/or infarction as contributors to the clinical deterioration will be made. Any imaging taken prior to the routine 24-hour imaging (which may be taken in a time window of 16-36 hours without becoming a protocol deviation) for this reason will be included in the analysis.

Hemorrhages will be classified clinically and radiologically according to the Heidelberg Bleeding Classification (see definitions section for complete description).[24]

7.2. Neurologic Evaluations

Repeat NIHSS determinations are performed in line with standard of care at 24 hours (-8/+12 hrs.) and at seven (7) days (-2/+3 days or discharge whichever is sooner) follow-up time points post-procedure. An additional NIHSS score should be obtained when any signs of neurologic deterioration occur or in the event of an ICH to assess the degree of deterioration. A certified examiner should perform all neurologic evaluations. Follow-up assessments will be conducted by blinded and certified study team member.

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8. Statistical Analysis

8.1. Study Design

The Envi™-SR study is a prospective, multi-center randomized adaptive design where the primary effectiveness endpoint will be assessed via a blinded evaluation of the Modified Rankin Scale (mRS). Up to 30 study centers may participate in this study. A pre-specified interim assessment for conditional power (CP) for potential sample size readjustment will be performed by the independent DMC after 50% of the minimum target ITT sample size (270/2: 135 patients) have been randomized and completed the day 90 evaluation or prematurely discontinue from the study. The purpose of this trial is to provide confirmatory clinical evidence that the Envi™-SR Thrombectomy Device provides benefits similar to those of the Control Devices for LVO strokes.

8.2. Sample Size Considerations

The objective of this trial is to demonstrate similar performance after treatment with the Envi™-SR device compared to the expected proportion of good outcomes at 90 days in the Control arm. The expected proportion of good outcomes in the Envi™-SR arm was estimated based on earlier results with Control. A -12.5% non-inferiority margin (NIM) will be used to examine the lower bound of the 1-sided 97.5% exact binomial confidence interval of the difference (Envi™-SR minus Control) in the proportion of patients with a 90-day mRS of 0-2. The null hypothesis and alternative hypothesis are presented below.

Ho: Envi™-SR – Control ≤ -12.5%

Ha: Envi™-SR – Control > -12.5%

If the lower bound of the 1-sided 97.5% exact binomial confidence interval of the difference (Envi™-SR minus Control) in the proportion of patients with a 90-day mRS of 0-2 is greater than -12.5%, then non-inferiority will be established.

The planning estimates for the Envi™-SR study considered the lower bound of the 2-sided 95% (asymptotic) confidence interval from the SWIFT PRIME[25] study for estimation (50.5%). Sample size estimates were prepared for this parallel design study assuming a non-inferiority margin of -12.5% (Envi™-SR successes [%] minus Control successes [%]). Under the alternative hypothesis, non-inferiority would be claimed if the lower bound of the 1-sided 97.5% confidence interval of the difference is less than the non-inferiority margin of -12.5%. All planning estimates are performed for the ITT population as this is the primary population for analysis.

For planning purposes, the estimated effectiveness of the Control device was based on a previously published meta-analysis of 5 randomized trials in which the effectiveness of endovascular thrombectomy over standard medical care was shown. This study was referred to as the HERMES collaboration.[26] Of the 633 included participants that received thrombectomy, 46.0% (291) achieved a good outcome based on an mRS score ≤ 2 at 90 days. The expected effectiveness of the Envi™-SR thrombectomy device was based on the SWIFT PRIME[25] study where 98 patients were treated with the Control FR (Flow Restoration) or Control 2 device. In total, 59 out of the total 98 patients who were treated achieved an mRS score less than or equal to 2. As the reported 60% patients with good outcome in the SWIFT PRIME[25] study might be an overestimation of the actual result, the lower bound of the 95% CI was calculated based on a normal approximation. The construction of a confidence interval around the estimate of SWIFT PRIME[25] yielded a 95% CI of [50.5% - 69.9%].

Target Sample Size

Assuming 46% of the Control patients and 50.5% of the Envi™-SR patients have an mRS score

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≤ 2 at 90 days, 270 total subjects (ITT) will be required.

Maximum Sample Size

If the gap narrows between the 2 randomized groups to 49.5% (Control) and 50.5% (Envi™-SR), 426 total patients (ITT) will be required (type 1 error rate of 2.5%, power of 80%). A loss to follow-up rate of 5% or less is expected. Missing data will be imputed as described in section 8.2.2. As multiple imputation could dampen the signal from the subject data that is imputed, an additional 5% of subjects may be added to compensate for any potential impact, leading to a total sample size of 448 subjects (ITT).

All estimates are performed based on the ITT population. However, all enrolled subjects (i.e., consented), including enrolled screen failures, will count toward the maximum sample size of 560 patients. The rate of enrolled screen failures is not expected to exceed 25%. Therefore, the maximum sample size for enrollment will be the ITT maximum sample size plus 25%, or 560 patients.

Additional Estimates

Estimates were also prepared under situations where the gap between arms remains consistent but both proportions shift to account for effects such as Additional Therapy methods. Sample sizes remain sufficient under these situations, see the SAP for additional detail.

Estimates were also prepared for the secondary endpoints. For the primary safety endpoint (sICH within 24 hours (-8/+12 hours) after the study procedure), the incidence of sICH is not expected to exceed 4% in either arm of the study. The total sample size required for 80% power, a type 1 error rate of 2.5%, and a non-inferiority margin of 7% is 318 patients.

For the proportion of patients with eTICI 2b50 or greater flow (single pass and after a maximum of 3 passes, the incidence is expected to be ~74% in both arms of the study. The total sample size required for 80% power, a type 1 error rate of 2.5%, and a non-inferiority margin of 12.2% is 408 patients.

Ninety days following the index stroke, mortality is not expected to be exceeded ~13.8% in both arms of the study. The total sample size required for 80% power, a type 1 error rate of 2.5%, and a non-inferiority margin of 10% is 390 patients.

8.2.1. Justification for the Non-Inferiority Margin for the Primary Effectiveness Endpoint

The inverse variance weighting method developed by Fleiss (1993) and later provided in Fleiss et al. (2003) was used to establish the non-inferiority margin.[27 28] There are five (5) randomized trials demonstrating the benefit of revascularization after ischemic stroke that form the basis of such analyses. Goyal et al. (2015) presented the results of the ESCAPE trial,[10] Berkhemer et al. (2015) presented the MRCLEAN trial,[29] Jovin et al. (2015) presented the results of the REVASCAT trial, [30] Campbell et al. (2015) presented the results of the EXTEND IA trial,[13] and Saver et al. (2015) presented the results of the SWIFT PRIME trial.[25] The five studies were combined by this method in the tables below. The first table provides the estimate unadjusted for heterogeneity and the second table adjusts the estimate for heterogeneity based on the value of Q. Only the test arm of the five trials are provided below with success being defined as having a 90-day modified Rankin Score of 0 to 2.

Table 8.1: Unadjusted Mean and 95% Confidence Limits on the Literature Rates

Study	N	X	Y_C	VAR[a]	W_C	$W_C Y_C$	W_C^2

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SWIFT PRIME	98	59	0.6020	0.0024448	409.036071	246.25641	167310.508
ESCAPE	120	64	0.5333	0.0020741	482.142857	257.142857	232461.735
REVASCAT	103	45	0.4369	0.0023885	418.669349	182.913793	175284.024
EXTEND IA	35	25	0.7143	0.0058309	171.5	122.5	29412.25
MRCLEAN	233	76	0.3262	0.0009433	1060.11876	345.789809	1123851.78
				SUM	1154.60287	2541.46703	1728320.29
					$\bar{Y}$	**LCL**	**UCL**
				C=5	0.4543	0.4154	0.4932
[a]The VAR term in the table is actually the standard error of the Y_C.							

In Table 8.2, the test of heterogeneity is computed and the adjustment if Q>C-1.

Table 8.2: Adjusted Mean and 95% Confidence Limits on the Literature Rates

Study	Y_C	$\bar{Y}$	$Y_C-\bar{Y}$	$(Y_C-\bar{Y})^2$	$W_C (Y_C-\bar{Y})^2$	W_C^*	$W_C^* Y_C^*$
SWIFT PRIME	0.6020	0.4543	0.1477	0.02182568	8.9275	44.7338	26.9316
ESCAPE	0.5333	0.4543	0.0790	0.00624537	3.0112	45.4881	24.2603
REVASCAT	0.4369	0.4543	-0.0174	0.00030319	0.1269	44.8467	19.5932
EXTEND IA	0.7143	0.4543	0.2600	0.06758963	11.5916	38.8492	27.7494
MRCLEAN	0.3262	0.4543	-0.1281	0.01641612	17.4030	47.9548	15.6419
				SUM Q=	41.0602	221.8726	114.1764
$\bar{W}$=	508.29341						
S_W^2=	109127.34			D_1=	0		
U=	1861.4188			D_2=	0.01990968		
				$\bar{Y}^*$	$SE(\bar{Y}^*)$	LCL	UCL
				0.5146	0.0671	0.3830	0.6462

Since Q>C-1, an adjustment was made to the mean success rate and the between study standard error has increased to 0.0671. This demonstrates that the upper and lower limits are 0.5146±0.1315 (1.96-0.0671). The variability between and within the five (5) studies is 0.13 (13%) and a margin of equivalence that size or smaller would be appropriate. The non-inferiority margin for this study will be set at -12.5%.

8.2.2. Missing and Censored Data

Missing data, which in this instance is defined as data that was not entered into the EDC system for analysis, may have an impact upon the interpretation of the trial data.

The primary presentation of the results for the primary and secondary endpoints using the ITT population will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. This procedure uses an iterative modeling approach to generate estimates for patients who withdraw prematurely, or the data is just not recorded, incorporating

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multivariate imputation by fully conditional specification (FCS) methods. The discriminant function method will be used for classification variables. With the function method of classification, the missing values will be imputed sequentially in the following order:

- Age: (≥67 and <67)
- Site of occlusion: ICA, MCA M1, MCA M2
- Baseline/Enrollment NIHSS score (<17 and ≥17)
- Prior IV t-PA usage (Yes / No)
- Time to symptom onset (≥6 hours and <6 hours)
- Baseline ASPECTS (6-7 and 8-10)

Each missing score will be imputed ten times to generate ten imputed complete datasets based on the Markov Chain Monte Carlo (MCMC) method with age, occlusion site, NIHSS score (<17 / ≥17), baseline ASPECTS (6-7 / 8-10), prior IV t-PA usage (yes / no), and time to symptom onset (≥4 hours / <4 hours) entered into the model following this sequential order. The imputed score will be rounded to the first decimal point for continuous variables. Proc MIANALYZE will be used to combine the imputed datasets to render an analysis of the binary outcomes for the results for the primary effectiveness and safety endpoints and the applicable 4 secondary endpoints. The relevant secondary endpoint analysis will follow the method outlined to calculate the odds ratio with the imputed dataset.

Additional sensitivity analyses will also be conducted as a secondary examination of the primary analysis using the last observation recorded following the procedure observation carried forward. A tipping point analysis will also be conducted.

If a patient did not have solicited adverse events of special interest [incidence by type of event] prior to withdrawing prematurely from the study, the patient will be considered as not having experienced the event.

Additional details for addressing partial and completely missing dates are addressed in the Statistical Analysis Plan.

8.3. Analysis Methods

8.3.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint of this study maps to the primary efficacy objective and addresses the following research question:

> *At 90 days (± 15 days) following the study index procedure, is the lower bound of the 1-sided 95% confidence interval of the difference (Envi™-SR minus Control) in global disability (mRS ≤ 2) above the a priori threshold of -12.5%? This is a 1-sided evaluation to establish non-inferiority.*

The hypothesis is that the proportion of good outcomes (mRS ≤ 2) at 90 days after treatment with the Envi™-SR thrombectomy device in patients with cerebral infarction is non-inferior to the rate of good outcome at 90 days after treatment with the Control device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.5% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- Ho: Treatment with Envi™-SR is inferior to treatment with Control for good outcomes defined as an mRS ≤ 2 at 90 days based on a non-inferiority margin of -12.5% (good outcome with Envi™-SR < [good outcome with Control – 12.5%]).

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- Ha: Treatment with Envi™-SR is non-inferior to treatment with Control for good outcome defined as an mRS ≤ 2 at 90 days based on a non-inferiority margin of -12.5% (good outcome with Envi™-SR ≥ [good outcome with Control – 12.5%])

The SAS code to generate these summary statistics and addressing missing mRS data at 90 days post-procedure is presented in the Statistical Analysis Plan. If the lower bound of the 1-sided 97.5% confidence interval of the difference (Envi™-SR minus Control) in global disability is numerically greater than -12.5%, Envi™-SR will be considered non-inferior to Control.

Additional therapies are defined in Section 3.5. The primary effectiveness endpoint will be derived 3 ways:

Method 1: mRS based on the observed results, independent of the use of additional therapies to retrieve the clot. Multiple imputation will be used to impute the mRS score for patients who become lost to follow-up prior to the 90 day evaluation.

Method 2: mRS based on the observed results for patients where additional therapies were not used to retrieve the clot. Subjects who required additional therapy for reperfusion failure or additional off-label therapies to retrieve the clot will be automatically treated as primary effectiveness endpoint failures. Multiple imputation will be used to impute the mRS score for patients who become lost to follow-up prior to the 90 day evaluation.

Method 3: mRS based on the observed results for patients where additional therapies were not used to retrieve the clot. Subjects who required any additional therapy to retrieve the clot will be automatically treated as primary effectiveness endpoint failures. Multiple imputation will be used to impute the mRS score for patients who become lost to follow-up prior to the 90 day evaluation.

An important consideration in requiring any patient who received additional therapy to retrieve the clot is acknowledging this is truly a random effect. The observed mRS at 90 days could indicate no difference in functional independence between the 2 randomized treatment groups, but the use of additional therapies could, by chance and chance alone, result in non-inferiority being achieved or lost. For this reason, Method 1 is the primary method for the derivation of the primary effectiveness endpoint for the study; Method 2 and Method 3 represent secondary derivations of the primary effectiveness endpoint.

Two (2) additional sensitivity analyses will be prepared to explore alternative methods for imputation for patients who are lost to follow-up (ref. Section 5.4) for the primary endpoint. The first sensitivity analysis will impute the baseline value for the 90-day result, functionally resulting in no change from baseline. The second sensitivity analysis will be conducted imputing the worst score at 90-days recorded for a patient within their respective treatment group for patients who are lost to follow-up. Additional details are provided in the SAP.

Additionally, as a final sensitivity analysis of the primary endpoint, a logistic model will be performed within the imputed datasets derived using multiple imputation. This model will incorporate the stratification variables specified in the randomization as covariates and with randomization group assignment. Under the guise of a sensitivity analysis, separate sub-group analysis will be prepared to examine factors that may have influenced the 90-day mRS scores.

8.3.2. Analysis of the Secondary and Tertiary Endpoints

If non-inferiority is achieved based on the primary endpoint, a hierarchical step-down approach will be used to test the secondary endpoints in rank order. The following secondary effectiveness endpoints will be compared between the two treatment arms:

1. The first secondary effectiveness endpoint will be an assessment of the mRS shift from baseline at 90 days (± 15 days) following the study index procedure. The Cochran–Mantel–

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Haenszel test will be used to derive the 95% confidence intervals for the overall odds ratio. If the 95% confidence intervals for the overall odds ratio does not contain 1, the conclusion will be that the mRS shift is not proportional between the 2 devices. This is a 2-sided evaluation of the odds ratio.

2. The second secondary effectiveness endpoint will be an assessment of the proportion of patients who achieve reperfusion measured using the expanded Thrombolysis in Cerebrovascular Infarction index (eTICI). Successful achievement of the endpoint is defined as achieving an eTICI score of 2b50 or greater [eTICI 2b50-3] in the target vessel following three or less passes of the randomized device (as adjudicated by Core Lab). If the lower bound of the 1-sided 97.5% confidence interval of the difference (Envi™-SR minus Control) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure is numerically greater than -12.1%, Envi™-SR will be considered non-inferior to Control. This is a 1-sided evaluation to establish non-inferiority.
3. The third secondary effectiveness endpoint will be an assessment of the proportion of patients in whom a successful First Pass Effect is achieved. Successful achievement of the endpoint is defined as achieving an eTICI First Pass Effect (FPE) defined as eTICI 2c-3 after a single pass (as adjudicated by Core Lab). If the lower bound of the 1-sided 97.5% confidence interval of the difference (Envi™-SR minus Control) in the proportion of patients with eTICI 2c or greater flow in the target vessel post- first pass is numerically greater than -12.1%, Envi™-SR will be considered non-inferior to Control. This is a 1-sided evaluation to establish non-inferiority.
4. The fourth secondary effectiveness endpoint will be an assessment of the proportion of patients in whom a successful Modified First Pass Effect is achieved. Successful achievement of the endpoint is defined as achieving an eTICI Modified First Pass Effect (mFPE) defined as eTICI 2b50-3 after a single pass (as adjudicated by Core Lab). If the lower bound of the 1-sided 97.5% confidence interval of the difference (Envi™-SR minus Control) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post- first pass is numerically greater than -12.1%, Envi™-SR will be considered non-inferior to Control. This is a 1-sided evaluation to establish non-inferiority.
5. The fifth secondary effectiveness endpoint will be an assessment of the proportion of subjects with Early Response defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1 at seven (7) days (-2/+3 days) or discharge, whichever is sooner. If the probability value from the 2-tailed Fisher's exact test is <0.05 and the proportion of patients with an NIHSS of 0 or 1, or improvement in the NIHSS of 10 points or more from the baseline (pre-procedure) score is greater in the Envi™-SR treatment arm compared to the control arm, the null hypothesis will be rejected and Envi™-SR will be considered superior to Control. This is a 2-sided evaluation of the proportions.

The details for analyzing the individual tertiary endpoints are presented in the SAP.

8.3.3. Subject Analysis Populations

The following populations have been defined for reconciliation and analysis: the Enrolled population, ITT (Intention to Treat) population, PP (Per Protocol) population, and the As-Treated populations.

See section 5.1 Enrollment for descriptions of the populations.

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8.3.4. Evaluating the Effect of Different Clinical Sites and Regions (US vs. OUS) and the Effect of Clinical Sites with Low Patient Enrollment

The method to be applied for examining the effect of different clinical sites will facilitate the generation of adjusted estimates to contrast against the unadjusted estimates. The adjusted estimates for the primary effectiveness and safety endpoints will introduce the effect of different clinical sites; the unadjusted estimates for the primary effectiveness and safety endpoints will only consider the randomized treatment assignment in the model. This sensitivity analysis will address the fundamental question relative to the effect of clinical sites and is considered more informative than simply adding an interaction term into the model for analysis. To provide further insight into the results, the model will be run with the interaction term retained for treatment and clinical site.

To assess the effect of small clinical sites, sites with lower enrollment will defines as having ≤2, 3, 4, 5, and 6 patients. For each dataset with small sites defined as having ≤2, 3, 4, 5, and 6 patients, a random effects model will be used to calculate the overall estimate adjusted by clinical site. The general framework of the random effects model will adjust for variability both among the clinical sites and variability within the clinical sites. The model that will be used to derive the estimates and the standard errors is presented in the SAP. This model will be used to assess the primary effectiveness and safety endpoints. From the solution for fixed effects, the exponentiation of the estimates and the standard errors will provide adjusted confidence limits to assess the effect adjusted for clinical sites.

To assess the effect of geographic location, a random effect model will be used to calculate the overall estimate adjusted by the location of the investigational site (US vs. OUS). The model that will be used to derive the estimates and the standard errors is presented in the SAP. This model will be used to assess the primary effectiveness and safety endpoints. From the solution for fixed effects, the exponentiation of the estimates and the standard error will provide adjusted confidence limits to assess the effect adjusted for geographic location.

The testing strategy and exact model for analysis will be included in the Statistical Analysis Plan (SAP).

Establishing a Pseudo-Site for the Analyses

Small sites (i.e., sites that have less than 2 patients for any of the treatment arms) will be identified and the following method will be used for combining the data. Data from all small sites will be combined to form a single site in order to obviate non-estimable situations (i.e., at least 2 observations are needed to estimate variance) in the evaluation of the performance of the device by site. Once combined, the pooled site will remain as such for all analyses for which a site interaction effect is determined. If the pooled smaller sites represent a single site that has more than twice as many patients as the largest single site, however less than 3 times as many patients, the small sites will be ranked by size and divided into 2 pooled assignments using an alternating sequence (ABABAB). If the pooled smaller sites represent a site that has more than three times as many patients as the largest single site, however less than 4 times as many patients, the small sites will be ranked by size and divided into 3 pooled assignments using an alternating sequence (ABCABCABC). This methodology will be applied, based on the initial pooling of the smaller sites.

8.3.5. Evaluating the Effect of Different Control Devices

The method to be applied for examining the effect of different control devices will facilitate the generation of adjusted estimates to contrast against the unadjusted estimates. The adjusted

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estimates for the primary effectiveness and safety endpoints will introduce the effect of different control devices; the unadjusted estimates for the primary effectiveness and safety endpoints will only consider the randomized treatment assignment in the model. This sensitivity analysis will address the fundamental question relative to the effect of the different devices and is considered more informative than adding an interaction term into the model for analysis. To provide further insight into the results, the model will be run with the interaction term retained for treatment and different control devices.

To assess the effect of different control devices used in the control arm of the study, a random effects model will be used to calculate the overall estimate adjusted for each of the 2 device types (Trevo and Solitaire). The model that will be used to derive the estimates and the standard errors is presented in the SAP. From the solution for fixed effects, the exponentiation of the estimates and the standard error will provide adjusted confidence limits to assess the effect.

8.3.6. Evaluating the Effect of Different Envi™-SR Device Sizes

The method to be applied for examining the effect of different Envi-SR device sizes will facilitate the generation of adjusted estimates to contrast against the unadjusted estimates. The adjusted estimates for the primary effectiveness and safety endpoints will introduce the effect of different Envi-SR device sizes; the unadjusted estimates for the primary effectiveness and safety endpoints will only consider the randomized treatment assignment in the model. This sensitivity analysis will address the fundamental question relative to the effect of the different Envi-SR device sizes and is considered more informative than adding an interaction term into the model for analysis. To provide further insight into the results, the model will be run with the interaction term retained for treatment and device size.

To assess the effect of different Envi-SR device sizes used in the study, a random effects model will be used to calculate the overall estimate adjusted for each of the device sizes. The model that will be used to derive the estimates and the standard errors is presented in the SAP. From the solution for fixed effects, the exponentiation of the estimates and the standard error will provide adjusted confidence limits to assess the effect.

8.3.7. Evaluating the Effect of Time Last Seen Well (0-6 hours and >6 to 24 hours)

The method to be applied for examining the effect of time last seen well (TLSW) will facilitate the generation of adjusted estimates to contrast against the unadjusted estimates. The adjusted estimates for the primary effectiveness and safety endpoints will introduce the effect of the time last seen well (0-6 hours and >6 to 24 hours); the unadjusted estimates for the primary effectiveness and safety endpoints will only consider the randomized treatment assignment in the model. This sensitivity analysis will address the fundamental question relative to the effect of the time last seen well (0-6 hours and >6 to 24 hours) and is considered more informative than adding an interaction term into the model for analysis. To provide further insight into the results, the model will be run with the interaction term retained for treatment and time last seen well (0-6 hours and >6 to 24 hours).

To assess the effect of the time last seen well (0-6 hours and >6 to 24 hours), a random effects model will be used to calculate the overall estimate adjusted for the discrete time segments. The model that will be used to derive the estimates and the standard errors is presented in the SAP. From the solution for fixed effects, the exponentiation of the estimates and the standard error will provide adjusted confidence limits to assess the effect.

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8.3.8. Deviations from the statistical plan

Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan that will include the statistical rationale for change.

9. Amendment to the Protocol

Only NeuroVasc Technologies is allowed to modify this protocol. The change will be in the form of a protocol revision or amendment. Any modification that potentially affects subjects' rights or safety must also be approved by the IRB/EC/REB and other regulatory agencies. In an emergency situation, where action is necessary to protect the life or physical wellbeing of the subject, a departure from the protocol for an individual subject may be allowed, and that departure will be for that subject only. In such circumstances, the investigator must notify the IRB/EC/REB and NeuroVasc Technologies and must describe the conditions necessitating the departure from the protocol and the outcome of the emergency intervention in a written report. NeuroVasc Technologies will determine whether the subject is to continue in the study or be considered a major protocol deviation.

10. Deviations from the Protocol

10.1. Protocol Deviation (Major)

A *major protocol deviation* is defined as an event that resulted in an increased risk to a subject or others; affected the right, safety or welfare of a subject; or affected the integrity of the study. Major Protocol deviations include, but are not limited to, the following list:

- Failure to obtain informed consent prior to patient enrollment
- Failure to treat subject per randomized treatment assignment
- Enrolled (i.e., consented) subject did not meet the inclusion/exclusion criteria
- Subject did not attend follow-up visit
- Source data permanently lost
- Introduction of additional therapy (including direct aspiration) prior to attempting revascularization with assigned treatment device for three passes.

10.2. Protocol Deviation (Minor)

Any other events that do not comply with the requirements of the protocol will be considered *Minor protocol deviations*.

Protocol deviations include, but are not limited to, the following list:

- Incorrect version of the informed consent form used.
- Follow-up visit was outside the required window.

All protocol deviations (major and minor) from the study protocol must be reported to the appointed NeuroVasc Technologies representative/ study monitor on a protocol deviation form, regardless of whether medically justifiable, pre-approved by NeuroVasc Technologies or taken to protect the subject in an emergency. In addition, the investigator is required to adhere to the IRB/EC/REB procedures for reporting protocol deviations.

Investigators must obtain prior approval from NeuroVasc Technologies before initiating deviations from the investigational protocol, except in situations where necessary to protect the life or physical well- being of a subject in an emergency situation, or situations beyond the investigator's control (such as subjects not attending scheduled follow-up visits, etc.). Approval

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for deviations shall be documented in writing and maintained in the investigator and clinical study files. All deviations will be reported to NeuroVasc Technologies, regardless of medical justification, pre-approval by NeuroVasc Technologies, or emergency nature. Subject-specific protocol deviations will be reported using the protocol deviation form eCRF. Non-subject-specific protocol deviations (e.g. unauthorized use of the investigational device in the US outside the study, unauthorized use of the investigational device in the US by a physician who has not signed the investigator agreement, etc.) shall be notified in writing to NeuroVasc Technologies. FDA regulations (21 CFR 812.140 (a) (4)) require investigators to maintain accurate, complete and current records, including documentation showing the dates of and reasons for each deviation from the protocol. Per 21 CFR 812.46 (a), failure to comply with the investigational plan may result in termination of the investigator's participation in the study.

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11. Device Accountability

NeuroVasc Technologies is responsible for the traceability of the study device (Envi™-SR) for this clinical investigation. NeuroVasc Technologies assumes responsibility for maintaining the following records:

- Quantity of the devices, the dates the devices are delivered to study sites.
- Lot numbers of all devices to be used for the study.
- Records of the shipment of the study devices and ancillary supplies to study sites.

NeuroVasc Technologies will ship devices only to qualified sites participating in the investigation which have the appropriate traceability and stock management controls in place (e.g., locked cabinet/storage space.) The appointed NeuroVasc Technologies representative/ study monitor will ensure the study site meets the record-keeping requirements for accountability and reconciliation of the study devices and ancillary supplies as part of the Site Initiation Visit. The investigator is responsible for proper storage of received devices and ancillary supplies at the hospital, and for maintaining a current device-tracking log for the duration of the study. The study monitor will review device storage conditions and the completion of the site's device tracking log. Reconciliation of device disposition will be documented. The names of all persons who received, used, or disposed of any device at the site will be recorded.

Records for the return of all study devices and ancillary supplies to NeuroVasc Technologies will be completed by the study site, verified by the appointed NeuroVasc Technologies representative /study monitor), and final disposition records will be maintained by NeuroVasc Technologies.

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12. Safety and Adverse Events

12.1. Safety and Adverse Event Terms

An **Adverse Event (AE)** is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

An **Adverse Device Effect (ADE)** is any untoward and unintended response to a medical device. This includes Serious Adverse Device Effects and any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, and any event resulting from a user error.

The term **All-cause Mortality** is utilized for death from any cause.

Procedure-related Mortality is utilized for death that occurs within a period of 7days after the procedure or prior to discharge.

Procedure Related Serious Adverse Events (PRSAE) is where the interventional procedure caused, or cannot be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.

A **Serious Adverse Event (SAE)** is an adverse event which:

1. Led to death,
2. Led to serious deterioration in the health of the subject, that either resulted in
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
3. 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 CIP, without serious deterioration in health, is not considered a serious adverse event.

A **Serious Adverse Device Effect (SADE)** is an Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event (only device related).

Unanticipated Adverse Device Effect (UADE) means 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.

Unanticipated Serious Adverse Device Effect (USADE) means any 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.

12.2. Clinical Events Committee (CEC)

An independent board consisting of stroke neurologists and/or neurointerventionalists who are not participating in the study will adjudicate serious adverse events in the study.

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The role of the CEC will be to adjudicate all Adverse Events of Special Interest (AE related to Endpoints). To be explicit, Safety Endpoints are repeated below. All AE that relate to these endpoints will be adjudicated by the CEC. An AE may relate to multiple Endpoints.

Adjudicate all hemorrhages identified by the Core Lab as symptomatic or asymptomatic based on the neurological status of the subject.

0. (1° Primary) Device-related or procedure-related symptomatic intracranial hemorrhage (sICH) at 24 hours (-8/+12 hours) post treatment defined by the Heidelberg Bleeding Classification[19] as read by the Core Lab and adjudicated by the CEC
1. Symptomatic intracranial hemorrhage (sICH) defined by the Heidelberg Bleeding Classification post-procedure (as read by the Core Lab and adjudicated by the CEC).
2. Asymptomatic intracranial hemorrhages (aICH) defined by the Heidelberg Bleeding Classification within 24 (-8/+12) hours post procedure (as read by the Core Lab and adjudicated by the CEC).

Adjudicate whether an AE is deemed attributable to the procedure, to the Envi™-SR, Adjuvant therapy (IV thrombolysis, thrombectomy), or from the natural course of the initial stroke.

3. Device and Procedure Related Serious Adverse Events (PRSAE) within seven (7) days (-2/+3 days) or discharge, whichever is sooner.
4. Device and Procedure Related Serious Adverse Events (PRSAE).
5. Device-related Serious Adverse Device Effects.

Adjudicate all deaths.

6. Procedure-related mortality at seven (7) days (-2/+3 days) or discharge, whichever is sooner.
7. Stroke-related mortality at 90 days (±15 days) post-procedure.
8. All-cause mortality at 90 days (±15 days) post-procedure.

Adjudicate all serious neurological events

9. Neurological deterioration – defined by an increase of four (4) points or more on the NIHSS score, at the time of diagnosis compared to immediately before worsening within seven (7) days (-2/+3 days) or discharge, whichever is sooner.

Continuous evaluation of available external data and/or knowledge, as presented at major congresses and /or published in peer-reviewed journals, which may have an impact on the adjudication and analysis of the reported events.

12.3. Data Monitoring Committee (DMC)

An independent board consisting of stroke neurologists and/or neurointerventionalist(s) and a statistician who are not participating in the study will monitor the adverse events and the occurrence rate in the study.

The role of the DMC will be to:

- Monitor all AE and establish specific “stopping rules” for the study.
- Make recommendations for revisions to the protocol regarding safety of the study.
- Periodically review and monitor aggregated and individual subject data related to safety, data integrity, scientific validity and overall conduct of the study, to ensure the rights,

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safety, and welfare of the study subjects.

- Monitor subject accrual and retention.
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or on the ethical conduct of the study.
- Ensure the confidentiality of the study data and the results of monitoring.

12.4. Event notification

12.4.1. Adverse Events (AE) and Adverse Device Effects (ADE)

All adverse events and adverse device effects shall be recorded on sponsor-provided adverse event eCRF. The safety assessments will consist of AE from the time the ICF is signed through Day 90 for those subjects treated, and to 24 hours for those subjects identified as angiographic screen failures. Adverse events and adverse device effects shall be recorded in the form of a diagnosis, rather than providing the various signs and symptoms for a particular health condition. The investigator or investigator- appointed study personnel will complete these eCRFs. Adverse event and other reporting should be provided to the sponsor according to the timelines listed in Table 12.1.

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Table 12.1: Investigator Reporting Requirements

Type of Report	Report To	Reporting Time Frame
UADE	• Sponsor • IRB/EC/REB	As soon as possible, but in no event later than 5 working days of knowledge to Sponsor and 10 working days to IRB/EC/REB, as applicable.
Death	• Sponsor • IRB/EC/REB, if required	Written reports (e.g., via e-mail) within 48 hours of knowledge.
AE (including SAE)	• Sponsor • IRB/EC/REB, if required	Within 5 working days of knowledge (Local EC/IRB/REB may require different reporting for AE or SAE) Per EC/IRB/REB requirement
Device Deficiency with clinical sequelae	• Sponsor • IRB/EC/REB, if required	Within 48 hours of knowledge via written communication. Return the investigational device to sponsor within 48 hours of knowledge.
Device Deficiency, no clinical sequelae	• Sponsor	Within 5 working days of knowledge. Return the investigational device to sponsor within 5 working days of knowledge.
Protocol Deviation(s): 1. To protect the life or physical well-being of a subject in an emergency 2. If an investigator uses a device without obtaining informed consent	• Sponsor • IRB/EC/REB	Within 5 working days of knowledge.
Protocol Deviation	• Sponsor • IRB/EC/REB, if required	Within 5 working days of knowledge. Per EC/IRB/REB requirement.
Withdrawal of EC/IRB/REB approval	• Sponsor	Within 5 working days of knowledge.
Progress report	• Sponsor • IRB/EC/REB	As required by EC/IRB/REB, but in no event less often than yearly.
Final Report	• Sponsor • IRB/EC/REB	As required by EC/IRB/REB, but within 3 months after termination or completion of the investigation or the investigator's part of the investigation.

Copies of related records and reports shall be provided to NeuroVasc Technologies upon request (PHI redacted). If the Investigator is made aware of any SAEs after Day 90, these should also be reported to NeuroVasc Technologies or its designee provided the SAE is considered related to the investigational device. The site would then provide a completed SAE form within one (1) business day and the event will be followed until resolution, or until adequate stabilization is met.

An AE that occurs after the ICF has been signed and before the treatment with the Envi™-SR has started is identified as a pretreatment AE (PTAE). This will include AEs occurring in those subjects identified as screening failures through the angiographic inclusion or exclusion criteria. An AE that occurs after treatment using Envi™-SR (or assigned device) has started will be considered a treatment emergent AE (TEAE). All AEs must be recorded and reported accordingly, whether they appear causally related to the interventional procedure, or not. Adverse events will be followed until the outcome is known or until the Investigator feels no further medical follow-up is warranted.

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All AEs will be reported verbatim as provided by the Investigator. The AEs will be categorized using MedDRA Coding of Adverse Events nomenclature Standardized nomenclature that will be ascertained includes lowest level and preferred MedDRA terms, MedDRA System Organ Class. All Adverse Events will be provided to the DMC for review on a periodic basis. Adverse Events are subject to adjudication as detailed in section 12.2.

Should potential AEs or ADEs be discovered during the study of which the investigator was not aware, the clinical research associate, study monitor, or Medical Monitor will provide relevant documentation within 10 days from becoming aware of the event for the investigator's review and submission to the IRB/EC/REB if applicable.

12.4.2. Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE)

The investigator should notify the appointed NeuroVasc Technologies representative/ study monitor of all SAEs and all SADEs immediately after becoming aware of the event. The investigator may also contact the appointed Medical monitor for assistance in determining whether or not the event in question is considered serious. Notification should be provided by completing all available fields of the adverse event eCRF or faxing or sending the form by e-mail to the appointed NeuroVasc Technologies representative and Medical Monitor if necessary.

SAE and SADE must be fully reported to sponsor within the timelines mentioned in Table 12.1. Reporting requirements for the local IRB/EC/REB may vary and all local requirements shall be followed in addition to the study requirements.

12.4.3. Reporting Unanticipated Adverse Device Effect (UADE)

The sponsor will report the results of an evaluation of any UADE to FDA and all reviewing IRB/EC/REBs and investigators within 10 working days from receiving notice of the UADE. An *ad hoc* review by the DMC will be held to determine if a potential UADE is an actual UADE.

12.4.4. Device Deficiency

All device deficiencies (as defined below) will be reported to sponsor within the timelines mentioned above in Table 12.1 and reported to the IRB/EC/REB as required.

- **Device failure:** A device has failed if it is used according to the labeling, including without limitation, instructions for use, and applicable standards of medical practice but does not perform according to the labeling and negatively impacts the treatment.
- **Device malfunction:** A device malfunction is a change in the function of the device that is not described in the labeling and that may or may not affect device performance.
- **Device misuse:** A misused device, i.e., one that is not used by the investigator (in the study) in compliance with applicable standards of medical practice, including without limitation, those described in the instructions for use and labeling, will not be considered a malfunction.

12.4.5. Electronic Data Capture (EDC) Recording

The Electronic Data Capture (EDC) program system will record all subject information including any specific incident details for all subjects in the study. This includes all AE, ADE, SAE, SADE, and UADE events. The program will also capture all subsequent interventions and/or treatments administered to the subject. The information is entered directly into the database by the Investigator or an assigned designate at each study site, who has been trained in the use of the

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program by NeuroVasc Technologies or a representative of NeuroVasc Technologies.

13. Site Initiation

NeuroVasc Technologies or a representative of NeuroVasc Technologies will conduct a training session with the study site team as described in Section 13.1.

Prior to enrolling subjects at a study site, the following documentation must be provided to NeuroVasc Technologies or a representative of NeuroVasc Technologies:

- IRB/EC/REB approval for the Protocol.
- IRB/EC/REB and NeuroVasc Technologies approved Informed Consent Form for the study.
- Investigator(s') curriculum vitae (CV).
- Financial Disclosure(s) for the PI and Sub/Co-I(s).
- Current/Valid Medical Licenses for the PI and Sub/Co-I(s).
- Signed Investigator's Agreement by all participating Investigators and Sub/Co-I(s) as applicable.
- Signed Clinical Study Agreement (CSA).
- Delegation of Authority (DOA) Log completed and signed by Investigator
- Training Log documentation to verify the appropriate study staff has been trained on the protocol, device, eCRFs and study conduct.
- Training certifications for NIHSS and mRS.

13.1. Training

Appropriate clinical site personnel at each investigational site, including Investigator, Sub/Co-Investigator(s), and Research Coordinator(s), will be trained to the protocol. To ensure proper device usage, data collection and protocol compliance, NeuroVasc Technologies will schedule a site initiation visit (SIV) at each site. Investigator/Site Personnel will undergo training prior to performing any study-related procedures. All training must be documented. Training to the protocol will include the following topics:

- Study objectives.
- Protocol review and compliance.
- Responsibilities and obligations of the investigator/study site team.
- Delegation of authority for study-related tasks.
- The Instructions for Use of the Envi™-SR.
- Informed Consent process, including any relevant IRB/EC/REB requirements.
- Techniques for identification of eligible subjects.
- Study documentation required (essential documents).
- Randomization system.
- Electronic Case Report Forms and completion instructions.
- Documentation of protocol deviations.
- Adverse, Serious Adverse Event Reporting.
- Product malfunction reporting.
- Image submission procedure.
- General guidelines for good clinical practices.
- Follow-up scheduling.
- Regulatory requirements.

Existing study site personnel who have been delegated new tasks and new study site personnel

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will undergo training to the protocol, as appropriate.

14. Study Monitoring

The study data will be monitored* regularly by a dedicated monitor to make sure that all data are correct. There will be a SIV, the first monitoring visit will occur as soon as possible after enrollment of the first subject followed by a visit after the fourth subject is enrolled during the enrollment phase. A minimum of one monitoring visit (per site) will be performed during the follow-up phase.

When the monitor requests additional data or clarification of data for the eCRF, the request must be answered completely before the next monitoring visit. The Investigator must sign all eCRFs. Completed eCRFs will be electronically signed off by the study monitor after they have been verified against source data. For SAEs or SADEs discovered during the study of which the investigator was not aware, NeuroVasc Technologies or the appointed NeuroVasc Technologies representative/study monitor will provide relevant documentation within 10 days from becoming aware of the event for the investigator's review and submission to the ethics committee, if applicable.

All sites both in the US and OUS will be subject to a monitoring visit with 100% source data verification (SDV) as soon as possible after the enrollment of the first subject. Monitoring will focus on correct adherence to the protocol and the complete and appropriate data entry. Continued participation in the study depends on satisfactory study compliance.

There will be a site closure visit to ensure all documentation is in place and all outstanding items have been addressed.

(*This study protocol and study monitoring plan will adhere to FDA's Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (released March 2020) as needed and when applicable.[31])

15. Data Collection

15.1. Data Management Responsibilities

The handling of data, including data quality assurance, will comply with regulatory guidelines (for example, GCP) and the sponsor's SOPs and work instructions. All steps and actions taken regarding data management and quality assurance will be documented in the sponsor's SOPs and data handling guidelines.

Completed eCRFs will be 100% verified against source data and visually checked by the study monitor for completeness, consistency, and legibility.

All adverse event terms recorded on the eCRF will be entered into the sponsor's safety database.

All data on the eCRFs will be entered into a validated database. Edit checks will be implemented to ensure data quality and accuracy. Responses to requests for further clarification of data recorded in the eCRF will be answered, dated, and electronically signed by the investigator. Changes will be implemented in the sponsor's database and the data review and validation procedures will be repeated as needed.

At the end of the study, the database will be locked, and the data will be released for reporting and statistical evaluation.

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15.2. Confidentiality

The investigator and institution involved in this study will only provide direct access to source data and documents to the sponsor, NeuroVasc Technologies, and to appropriate authorities for the purposes of monitoring, audit, ethics committee review or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing.

All subject data will always be treated with strict adherence to professional standards of confidentiality. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

15.3. Electronic Case Report Forms

Data collected for each subject will be recorded on an electronic Case Report Form (eCRF) provided by NeuroVasc Technologies Instructions for proper completion will be provided. The investigator is responsible for ensuring that all sections of each eCRF are complete and correct and that those entries can be verified against source data (such as patient hospital files or programmer printouts).

15.4. Source Documentation

Investigators are required to prepare and maintain adequate and accurate case histories, recording all observations and other data pertinent to the investigation on each subject.

15.5. Data record keeping

All study material shall be stored for at least 10 years and only destroyed after written approval from NeuroVasc Technologies.

16. Audits/Inspections

An independent audit by NeuroVasc Technologies or external regulatory agencies from the investigator's own country or from abroad may take place at any time during or after the study. This may include on- site inspections and source data verification at the investigator's hospital. If the authorities announce inspection, the investigator should inform NeuroVasc Technologies immediately.

17. Criteria for Terminating Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Investigators and associated IRBs/ECs will be notified in writing in the event of termination.

Possible reasons for study termination include, but not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue development of the device.

18. Criteria for Terminating a Study Site

The sponsor reserves the right to stop the enrollment of subjects at a study site at any time after the SIV if no subjects have been enrolled or if the site has multiple or severe protocol deviations without justification or fails to follow remedial actions. Possible reasons for terminating a study

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center include, but not limited to:

- Insufficient enrollment rate i.e., less than 1 subject in a 10-week period.
- Repeated deviations of inclusion/exclusion criteria
- Repeated failure to complete CRFs in a timely manner.
- Failure to obtain Informed Consent.
- Failure to report serious adverse events within 24 hours of knowledge.
- Loss of (or unaccounted for) investigational product inventory.

19. Study Finances

A Clinical Investigation Agreement (or equivalent) will be prepared by NeuroVasc Technologies, which will be signed by the participating study site. This agreement describes the legal conditions, conditions for financial compensation, and reimbursement details for the co-operation between NeuroVasc Technologies and the Investigator in this study.

20. Medicare Beneficiaries

In this study, subjects who are at least 18 years old at time of consent, with no upper limit of age, are eligible for study enrollment if all other study entry criteria are satisfied. Based on literature review and current medical practice, a significant proportion of the subjects enrolled into this study are expected to be Medicare eligible. For example, in a large scale study of a similar subject population of 500 subjects, it was reported that the median age was 65 years.[8]In another similar subject population study of 316 subjects, it was reported that the median age in the interventional arm was 71 years and the control arm was 70 years.[9] The results of this current study are therefore expected to be generalizable to the Medicare beneficiary population on the basis of age.

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21. Study Management

The chart in Figure 21-1 outlines the supervisory bodies that will oversee all clinical study activities including protocol development and protocol amendment during study conduct. NeuroVasc Technologies or representative will perform monitoring at each site to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted according to FDA regulations. The Study Principal Investigators will be available to provide consultation to study investigators regarding any technical and procedural issues that may arise during the treatment procedure.

Figure 21-1: Supervision responsibility for the Clinical Investigation

Executive Steering Committee	Permanent members: • Co PI US • Co PI OUS • Sponsor Representative Rotating based on volume enrollment: • Top PI(s) Neurointerventionalists • Site(s) Neurointerventionalists
Data Monitoring Committee (DMC)	Minimum members: • One (1) Independent DMC Chair • One (1) Independent Neurologist • One (1) Independent Clinician • One (1) Independent Biostatistician
Clinical Events Committee (CEC)	Minimum members: • One (1) Independent CEC Chair • One (1) Independent Neurologist • One (1) Independent Clinician

22. Clinical study insurance

Product liability insurance is in place for the Envi™-SR when used as described under the IFU. NeuroVasc Technologies maintains appropriate product liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. An insurance statement/ certificate will be provided to the IRB/EC/REB.

23. Publications Plan

All information concerning the Envi™-SR or NeuroVasc Technologies (e.g., patent applications, manufacturing processes, basic scientific data, and materials information) supplied to the investigator by NeuroVasc Technologies and not previously published is considered confidential and shall remain the sole property of NeuroVasc Technologies. The investigator agrees to use this information only in accomplishing the study and will not use it or the data generated from the study for other purposes without first obtaining the written consent of NeuroVasc Technologies.

It is understood that NeuroVasc Technologies will use the information developed in this clinical study as part of a development program for the Envi™-SR, and therefore may disclose this information as required to other NeuroVasc Technologies investigators or to government regulatory agencies. The investigator understands that she/he has the obligation to provide

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complete test results and all data developed during this study to NeuroVasc Technologies or its designate.

Every effort will be made to publish the results of this study irrespective of whether the findings are in favor of the Envi™-SR. To this end, and to avoid publication bias, the NV-001 study will be registered, on the clinicaltrials.gov database.

A Publications Committee will be formed to review and publish the data from the study. This committee will include the co-principal investigators, and one representative of the sponsor. The committee will create a publication policy describing in detail the organization of authorship. The Publications Committee will write/review all drafts of abstracts and full-length manuscripts and will choose the appropriate journal (for manuscripts) or meeting (for abstracts) for submission. For clarity, the Co-Principal Investigators will have the final decision making and editorial rights on the paper submitted for publication.

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Appendix A: Terms and Definitions

For the purposes of this protocol the following terms and definitions apply.

Term	Definition
Adverse Device Effect (ADE)	Any untoward and unintended response to a medical device. This includes Serious Adverse Device Effects and any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, and any event resulting from a user error. Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. ISO 14155:2011
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices. Note 4: Severity of AEs defined in section 12.1 for reference 21CFR312.32, ISO 14155:2011
Adverse Events of Special Interest	Adverse Events that relate to the Endpoints • sICH up to 90 days • aICH up to 24 hour timepoint • Any AE at least possibly related to procedure or device • Neurological deterioration up to 7 days or discharge (whichever is earlier) • All-cause mortality (including stroke-related and procedure-related mortality)
All-cause Mortality	The term is utilized for death from any cause.
Asymptomatic ICH (aICH)	New intracranial hemorrhage that has no implications for prognosis or change in management, and there is no substantive change in the patient's neurological status as defined by the Heidelberg Bleeding Classification. See Heidelberg Bleeding Classification for additional criteria.
As-Treated population	The As-Treated population is a subset of the ITT population that and will consist of all subjects randomized into the study analyzed according to the treatment received.
Audit	Systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted,

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	and the data recorded, analyzed and accurately reported, according to the Protocol, standard operating procedures, this International Standard and applicable regulatory requirements.
Clinical Investigation	Systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device. Note1: "Clinical trial" or "clinical study" are synonymous with "clinical investigation".
Clinical Protocol	Document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.
Clinical Investigation Report	Document describing the design, execution, statistical analysis and results of a clinical investigation.
Clinical Performance	Behavior of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s).
Contract Research Organization (CRO)	Person or organization contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions.
Control Device	Reference Section 6.2 (Table 6.1)
Coordinating Investigator	Investigator who is appointed by the sponsor to coordinate work in a multicenter clinical investigation.
Data Monitoring Committee (DMC)	Independent committee established by the sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation.
Deviation	See Protocol Deviation
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.
Device-related or procedure-related symptomatic intracranial hemorrhage (sICH)	sICH adjudicated by the CEC to be related to therapeutic intervention (either definite or probable) as defined by the Heidelberg Bleeding Classification.
Early Response	A NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1
Enrolled	All consecutive patients with a signed Informed Consent Form (ICF) will be considered part of the enrolled population.
eTICI	Refers to the expanded Thrombolysis in Cerebral Infarction scale.[19] **Score/Grade** | **Criteria** **0** | No reperfusion

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<table>
<tr><td></td><td>
<table>
<tr><td>1</td><td>Reduction in thrombus without filling of distal arterial branches</td></tr>
<tr><td>2a</td><td>Reperfusion in less than half the territory</td></tr>
<tr><td>2b50</td><td>Reperfusion in 50–66% of the territory</td></tr>
<tr><td>2b67</td><td>Reperfusion in 67–89% of the territory</td></tr>
<tr><td>2c</td><td>Extensive reperfusion in 90–99% of the territory</td></tr>
<tr><td>3</td><td>Complete or full reperfusion</td></tr>
</table>
</td></tr>
<tr><td>The Heidelberg Bleeding Classification</td><td>The Heidelberg Bleeding Classification is a process to categorize intracranial hemorrhage into sICH or aICH based on both a pure radiological classification scheme and a combined radiological-symptomatic classification scheme. This process is detailed in von Kummer R et al.[24]</td></tr>
<tr><td>Informed consent process</td><td>Process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation.

Note 1: Informed consent is documented by means of a written, signed and dated informed consent form.</td></tr>
<tr><td>Intracranial Hemorrhage</td><td>Defined per the Heidelberg Bleeding Classification
<table>
<tr><th colspan="3">Anatomic Description of Intracranial Hemorrhages</th></tr>
<tr><th>Class</th><th>Type</th><th>Description</th></tr>
<tr><td>1</td><td colspan="2">Hemorrhagic transformation of Infarcted brain tissue</td></tr>
<tr><td>1a</td><td>HI1</td><td>Scattered small petechiae, no mass affect</td></tr>
<tr><td>1b</td><td>HI2</td><td>Confluent petechiae, no mass effect</td></tr>
<tr><td>1c</td><td>PH1</td><td>Hematoma within infarcted tissue, occupying <30%, no substantive mass effect</td></tr>
<tr><td rowspan="2">2</td><td colspan="2">Intracerebral hemorrhage within and beyond infarcted brain tissue</td></tr>
<tr><td>PH2</td><td>Hematoma occupying 30% or more of the Infarcted tissue, with obvious mass effect</td></tr>
<tr><td>3</td><td colspan="2">Intracerebral hemorrhage outside the infarcted brain tissue or Intracranial-extracerebral hemorrhage</td></tr>
<tr><td>3a</td><td colspan="2">Parenchymal hematoma remote from infarcted brain tissue</td></tr>
<tr><td>3b</td><td colspan="2">Intraventricular hemorrhage</td></tr>
<tr><td>3c</td><td colspan="2">Subarachnoid hemorrhage</td></tr>
<tr><td>3d</td><td colspan="2">Subdural hemorrhage</td></tr>
</table>
</td></tr>
<tr><td>Investigator</td><td>Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation-related decisions.

Note 1: An individual member of the investigation site team can also be called “sub-investigator” or “co-investigator”.</td></tr>
<tr><td>Investigator's Brochure (IB)</td><td>Compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation.</td></tr>
</table>

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<table>
<tr><td>IV t-PA Failure</td><td>Failure of IV t-PA is defined as angiographic evidence of persistent target vessel occlusion 60 minutes or more after initiation of IV t-PA.</td></tr>
<tr><td>Legally Authorized Representative (LAR)</td><td>Individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical investigation.</td></tr>
<tr><td>Malfunction</td><td>Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP</td></tr>
<tr><td>Modified Rankin Score</td><td>Measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.
<table>
<tr><th>Score</th><th>Description</th></tr>
<tr><td>0</td><td>No symptoms at all</td></tr>
<tr><td>1</td><td>No significant disability despite symptoms; able to carry out all usual duties and activities</td></tr>
<tr><td>2</td><td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td></tr>
<tr><td>3</td><td>Moderate disability; requiring some help, but able to walk without assistance</td></tr>
<tr><td>4</td><td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td></tr>
<tr><td>5</td><td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td></tr>
<tr><td>6</td><td>Dead</td></tr>
</table>
NOTE: Envi™-RCT will utilize the Rankin Focused Assessment—Ambulation (RFA-A) form which is based on mRS as described by van Swieten.[1]

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. ”Interobserver agreement for the assessment of handicap in stroke patients.” Stroke 1988;19(5):604-7

RFA-A reference:

Patel RD, Starkman S, Hamilton S, Craig S, Grace A, Conwit R, Saver JL. The Rankin Focused Assessment-Ambulation: A Method to Score the Modified Rankin Scale with Emphasis on Walking Ability. J Stroke Cerebrovasc Dis. 2016 Sep;25(9):2172-6. doi: 10.1016/j.jstrokecerebrovasdis.2015.10.030. Epub 2016 Jul 20. PMID: 27450385.[32]</td></tr>
<tr><td>Modified Thrombolysis in Cerebrovascular Infarction (mTICI)</td><td>mTICI will be defined as the mTICI scale inclusive of the 2c rating for the purposes of this study, see reference [33].

NOTE: The mTICI scale is not intended to be used for this study</td></tr>
<tr><td>Monitoring</td><td>Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this International Standard, and the applicable regulatory requirements.</td></tr>
<tr><td>Neurological deterioration</td><td>An increase of four (4) points or more on the NIHSS score at the time of diagnosis compared to immediately before worsening</td></tr>
</table>

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Pass	The deployment and retrieval of a device while open through a target artery with occlusion. A deployment and resheathing with minimal movement (i.e., less than 10mm) does not constitute a Pass.
Point of Enrollment	Time at which a subject or LAR signs and dates the informed consent form.
Principal Investigator	An individual who actually conducts a study (i.e., under whose immediate direction the device is dispensed to a subject.) In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. Note 1: Also known as the Site PI
Procedure Related Serious Adverse Events (PRSAE)	A serious adverse event where the interventional procedure caused, or cannot be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event. Consisting of: • Vascular perforation • Intramural arterial dissection • Embolization to a new territory • Access site complication requiring surgical repair or blood transfusion • Intra-procedural mortality • Device failure (*in-vivo* breakage) • Any other SAE adjudicated by the CEC to be related to the procedure
Procedure-related Mortality	The term utilized for death that occurs within a period of 7 days after the procedure or prior to discharge.
Protocol Deviation	Instance(s) of failure to follow, intentionally or unintentionally, the requirements of the Protocol. Note 1: Includes Minor and Major Note 2: Protocol Deviation(s) listed below are required to be reported to the EC/IRB/REB: 1. To protect the life or physical well-being of a subject in an emergency 2. If an investigator uses a device without obtaining informed consent
Recruitment	Active efforts to identify subjects who may be suitable for enrollment into the clinical investigation.
Serious Adverse Device Effect (SADE)	Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Adverse Event (SAE)	Adverse event that a. Led to death, b. Led to serious deterioration in the health of the subject, that either resulted in 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c. Led to fetal distress, fetal death or a congenital abnormality or birth defect

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<table>
<tr><td></td><td>Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.</td></tr>
<tr><td>Source Data</td><td>All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.</td></tr>
<tr><td>Source Document</td><td>Printed, optical or electronic document containing source data.

EXAMPLES Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.</td></tr>
<tr><td>Sponsor</td><td>Individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation.</td></tr>
<tr><td>Subject</td><td>Individual who participates in a clinical investigation.</td></tr>
<tr><td>Symptomatic ICH (sICH)</td><td>Symptomatic ICH is a clinical event caused by intracranial hemorrhage. The determination of sICH involves an imaging and clinical adjudication per the Heidelberg Bleeding Classification. sICH to be reported as defined in Step 6: Definite and probable hemorrhage shall be classified as symptomatic.
<table>
<tr><th>Step</th><th>Description</th></tr>
<tr><td rowspan="3">1</td><td>Brain Imaging</td></tr>
<tr><td>Scheduled according protocol within 48 h after treatment</td></tr>
<tr><td>Unscheduled triggered by symptoms suggestive of intracerebral hemorrhage</td></tr>
<tr><td>2</td><td>Independent and blinded review of imaging (i.e. Core Lab)</td></tr>
<tr><td>3</td><td>Anatomic description of intracranial hemorrhages (see ICH)</td></tr>
<tr><td>4</td><td>Adjudication of the cause of neurological deterioration in the presence of intracranial hemorrhage</td></tr>
<tr><td rowspan="6">4a</td><td>sICH: New intracranial hemorrhage detected by brain imaging associated with any of the item below:</td></tr>
<tr><td>≥4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate pre-deterioration neurological status</td></tr>
<tr><td>≥2 point in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic but the patient will not have worsening of 4 points on the NIHSS score</td></tr>
<tr><td>Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention.</td></tr>
<tr><td>Absence of alternative explanation for deterioration</td></tr>
<tr><td>4b</td><td>aICH: new hemorrhage that has no implications for prognosis or change in management, and there is no substantive change in the patient’s neurological status</td></tr>
<tr><td rowspan="4">5</td><td>Establishing the relatedness of deterioration and imaging findings</td></tr>
<tr><td>In patients with neurological deterioration the relationship between clinical deterioration as defined in 4a and the hemorrhagic event is</td></tr>
<tr><td>Definite: if any intracranial hemorrhage is the dominant brain pathology on imaging causal for deterioration</td></tr>
<tr><td>Probable: in the presence of PH2, even if the ischemic infarct may have contributed to deterioration.</td></tr>
</table>
</td></tr>
</table>

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		Possible: in the presence of HI2, PH1, rPH, IVH, SAH, SDH, even if ischemic infarct may have contributed predominantly to the deterioration
		Unlikely: in the presence of HI1
	6	Categories for trial or registry reporting
		Definite and probable: hemorrhage shall be classified as symptomatic
		Possible and unlikely: hemorrhage shall be classified as asymptomatic
	7	Adjudication of relatedness of intracranial hemorrhage (symptomatic and asymptomatic) to therapeutic intervention
		Relatedness is defined by
		Treatment with thrombolytic agents (IV or IA) within the last 24 h
		Area of hemorrhage compatible with endovascular complication (regional and temporal relationship)
		Documented complication of angiographic procedure
		Levels of certainty of relatedness
		Definite: observed procedural complication e.g., perforation of intracranial artery
		Probable: treatment within last 24 h. PH, symptomatic or asymptomatic
		Possible: treatment within last 24 h. HI, symptomatic, or asymptomatic
		Unrelated: no therapeutic intervention during the last 24 h before detection of hemorrhage
		Hemorrhage is spontaneous. Any anatomic type, symptomatic or asymptomatic

Thrombolysis in Cerebrovascular Infarction (TICI)	Not intended to be used, see reference.[34]
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. 21CFR812.3
Unanticipated Serious Adverse Device Effect (USADE)	Any 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
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Note 1: Use error includes slips, lapses, and mistakes. Note 2: An unexpected physiological response of the subject does not in itself constitute a use error. ISO 14971:2007
Vulnerable Subject	A vulnerable subject is an Individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless

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	persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

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Appendix B: Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, Korea, October 2008

A. Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other subjects in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

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10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. Principles for All Medical Research

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. The committee may make no change to the protocol without consideration and approval.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

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17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

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26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research. Research not in accordance with the principles of this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo

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is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo, or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

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Appendix C: Potential Adverse Events

23.1. Typically Reported Serious Adverse Events (SAE)

The tables below list all SAEs that are typically reported in the literature referenced for predicate stent-like mechanical thrombectomy devices. These SAEs may be the result of the stroke, underlying illnesses, treatment with IV t-PA, procedural events, or device-related events.

Data are based on SWIFT PRIME, TREVO2, REVASCAT, ESCAPE, DAWN, and DEFUSE3 trial data.

Very Likely [Very Common] Typically Reported Serious Adverse Events (50% to 100%)		
SAE	**Details**	**Upper limit reported (%)**
No individual Serious Adverse Events reported at a rate of 50% to 100%		
Likely [Common] Typically Reported Serious Adverse Events (20% to 49%)		
SAE	**Details**	**Upper limit reported (%)**
Death (all-cause)	90 days post-procedure	33%

Less Common Typically Reported Serious Adverse Events (1% to 20%)		
SAE	**Details**	**Upper limit reported (%)**
Neurological worsening	-	15.5%
Hematoma at access site	-	10.7%
Death	0-7 days post-procedure	9.7%
Embolization to a previously uninvolved territory	-	7.6%
Symptomatic intracerebral hemorrhage	SITS-MOST, ECASS II, other	6.5%
Subarachnoid hemorrhage	-	4.9%
Arterial perforation	-	4.9%
Parenchymal hematoma	PH1	4.0%
	PH2	8.7%
Arterial dissection	-	3.9%

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23.2. Serious Adverse Events (SAE) per medDRA terminology

The tables below list all SAEs that are reported in the literature referenced for predicate stent-like mechanical thrombectomy devices or treatment with IV t-PA. These SAEs may be the result of the stroke, underlying illnesses, treatment with the control (IV t-PA), procedural events, device-related events, or may be random occurrences.

Data is based on SWIFT PRIME (both arms) and TREVO2 (Trevo arm) trial data, with the intention to treat population.

Very Likely [Very Common] Serious Adverse Events (50% to 100%)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**
No Serious Adverse Events reports at a rate of 50% to 100%		
Likely [Common] Serious Adverse Events (20% to 49%)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**
No Serious Adverse Events reports at a rate of 20% to 49%		

Less Common Serious Adverse Events (1% to 20%)					
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**Upper limit reported (%)**
Blood and lymphatic system disorders	Anaemia †	3.1%	Gastrointestinal disorders	Gastrointestinal haemorrhage †	1.0%
Cardiac disorders	Acute myocardial infarction †	1.0%		Ileus †	2.0%
	Atrial fibrillation †	1.0%		Intestinal ischaemia †	1.0%
	Bradycardia †	1.0%		Lower gastrointestinal haemorrhage †	1.0%
	Cardiac arrest †	2.0%		Occult Blood †	1.1%
	Cardiac failure congestive †	1.0%	General disorders	Drug Reaction †	1.1%
	Cardiopulmonary Arrest †	1.1%		Events With an Outcome of Death †	1.1%
	Chest Pain †	2.3%		Fever †	0.0%
	Congestive Heart Failure †	1.1%		Positive Cultures †	1.1%
	Hypotension – Sustained - Tx †	2.3%	Infections and infestations	Clostridium colitis †	1.0%
	Intracardiac thrombus †	2.0%		Endocarditis †	2.0%
	Ischaemic cardiomyopathy †	1.0%		Escherichia sepsis †	1.0%
	Myocardial infarction †	1.0%		Parotitis †	1.0%
	Sick sinus syndrome †	1.0%		Pneumonia †	1.0%
	Tachycardia †	2.1%		Respiratory syncytial virus infection †	1.0%
Injury, poisoning and procedural complications	Carotid artery restenosis †	1.0%		Sepsis †	2.1%
	Fall †	1.0%		Septic shock †	1.0%
	Joint dislocation †	1.0%	Metabolism and nutrition disorders	Electrolyte Imbalance †	1.1%
	Procedural vomiting †	1.0%		Other †	1.1%
	Vascular pseudoaneurysm †	1.0%	Musculoskeletal and connective tissue disorders	Joint/Extremity Pain †	1.1%

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Less Common Serious Adverse Events (1% to 20%)					
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**Upper limit reported (%)**
Nervous system disorders	Brain oedema †	11.4%	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Appendix cancer †	1.0%
	Cerebral haemorrhage †	1.0%		Pancreatic carcinoma metastatic †	1.0%
	Convulsion †	1.0%	Nervous system disorders	Intraventricular haemorrhage †	1.1%
	Dysphagia (Difficulty Swallowing) †	1.1%		Ischaemic stroke †	6.2%
	Haemorrhagic transformation stroke †	4.1%		Late ICH †	2.3%
	Headache †	1.1%		Neurologic Decline †	5.7%
	Hydrocephalus †	1.1%		Progression of index Stroke †	9.1%
	ICH – HI -2 †	1.1%		SAH †	3.4%
	ICH – PH1 †	5.7%		Status epilepticus †	1.0%
	ICH – PH2 †	3.4%		Stroke in evolution †	8.2%
	Intracranial aneurysm †	1.0%		Transient Ischemic Attack (TIA) †	2.3%
	Intracranial pressure increased †	1.0%		Unresponsiveness †	1.1%
Psychiatric disorders	Mental status changes †	1.0%		Vasculitis cerebral †	1.0%
Renal and urinary disorders	Haematuria †	1.0%	Respiratory, thoracic and mediastinal disorders	Acute respiratory failure †	1.0%
	Renal failure acute †	3.1%		Chronic obstructive pulmonary disease †	1.0%
	Renal failure †	1.0%		Haemoptysis †	1.0%
	Renal infarct †	1.0%		Hypoxia †	1.0%
	Urinary Tract Infection †	1.1%		Pleural Effusion †	1.1%
Skin and subcutaneous tissue disorders	Other †	1.1%		Pneumonia aspiration †	2.3%
Surgical and medical procedures	Access Site Complication †	2.3%		Pulmonary embolism †	1.1%
Vascular disorders	Arterial rupture †	1.0%		Respiratory arrest †	1.0%
	Deep vein thrombosis †	3.4%		Respiratory distress †	8.0%
	Embolism arterial †	1.0%		Respiratory failure †	3.4%
	Femoral artery embolism †	1.0%		Shortness of Breath †	1.1%
	Haematoma †	1.0%		Tachypnea †	1.1%
	Hypotension †	3.1%			
	Peripheral artery thrombosis †	1.0%			
	Vascular occlusion †	1.0%			
† Events were collected by systematic assessment					

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23.3. Adverse Events (AE) per medDRA terminology

This table lists all AEs that are reported in the literature referenced for predicate stent-like mechanical thrombectomy devices or treatment with IV t-PA. These AEs may be the result of the stroke, underlying illnesses, treatment with the control (IV t-PA), procedural events, device-related events, or may be random occurrences. Data is based on SWIFT PRIME (both arms) and TREVO2 (Trevo arm) trial data, with the intention to treat population.

Very Likely [Very Common] Adverse Events (50% to 100%)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**
No Adverse Events reports at a rate of 50% to 100%		
Likely [Common] Adverse Events (20% to 49%)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**
Nervous system disorders	Haemorrhagic transformation stroke †	40.2%
Infections and infestations	Urinary tract infection †	29.9%

Less Common Adverse Events (1% to 20%)					
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**Upper limit reported (%)**
Blood and lymphatic system disorders	Anaemia †	15.9%	Ear and labyrinth disorders	Vertigo †	1.0%
	Haemorrhagic anaemia †	1.0%			
	Heparin-induced thrombocytopenia †	1.0%	Endocrine disorders	Hyperthyroidism †	1.0%
	Leukocytosis †	6.1%		Hypothyroidism †	1.0%
	Thrombocytopenia †	1.0%	Eye disorders	Conjunctival haemorrhage †	1.0%
Cardiac disorders	Acute myocardial infarction †	1.0%		Dry eye †	1.0%
	Atrial fibrillation †	10.2%		Eye haemorrhage †	1.0%
	Atrial flutter †	1.0%		Optic neuropathy †	1.0%
	Atrial thrombosis †	1.0%		Photopsia †	1.0%
	Atrioventricular block first degree †	1.0%		Visual impairment †	2.0%
	Bradycardia †	7.2%	Gastrointestinal disorders	Abdominal pain lower †	1.0%
	Cardiac arrest †	2.0%		Abdominal pain upper †	1.0%
	Cardiac failure congestive †	1.0%		Abdominal pain †	1.0%
	Cardiac failure †	1.0%		Constipation †	18.4%
	Cardiomyopathy †	1.0%		Dental caries †	1.0%
	Intracardiac thrombus †	2.0%		Diarrhoea †	4.1%
	Ischaemic cardiomyopathy †	1.0%		Dyspepsia †	1.0%
	Myocardial infarction †	1.0%		Dysphagia †	15.9%
	Palpitations †	2.0%		Faecal incontinence †	1.0%
	Sick sinus syndrome †	1.0%		Gastritis †	1.0%
	Sinus arrest †	2.0%		Gastrointestinal haemorrhage †	1.0%
	Supraventricular tachycardia †	2.0%		Gastrooesophageal reflux disease †	1.0%
	Tachycardia †	9.3%		Haematemesis †	2.1%
	Ventricular tachycardia †	2.1%		Haemorrhoidal haemorrhage †	1.0%
General disorders	Application site pruritus †	1.0%		Haemorrhoids †	1.0%

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Less Common Adverse Events (1% to 20%)					
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**Upper limit reported (%)**
General disorders	Catheter site haematoma †	1.0%	Gastrointestinal disorders	Ileus †	2.0%
	Catheter site haemorrhage †	1.0%		Intestinal ischaemia †	1.0%
	Catheter site induration †	1.0%		Lower gastrointestinal haemorrhage †	1.0%
	Catheter site inflammation †	1.0%		Melaena †	1.0%
	Chest pain †	1.0%		Mouth haemorrhage †	1.0%
	Cyst †	1.0%		Nausea †	9.2%
	Discomfort †	1.0%		Oesophageal stenosis †	1.0%
	Extravasation †	1.0%		Oral pain †	1.0%
	Fatigue †	4.1%		Retroperitoneal haematoma †	1.0%
	Impaired healing †	1.0%		Salivary hypersecretion †	1.0%
	Influenza like illness †	1.0%		Swollen tongue †	1.0%
	Local swelling †	2.1%		Vomiting †	9.1%
	Oedema peripheral †	4.1%	Hepatobiliary disorders	Cholecystitis acute †	1.0%
	Pain †	5.1%		Cholelithiasis †	1.0%
	Polyp †	1.0%		Cholestasis †	1.0%
	Positive Cultures †	3.4%		Hepatic cyst †	1.0%
	Pyrexia †	9.2%	Immune system disorders	Drug hypersensitivity †	2.1%
	Systemic inflammatory response syndrome †	1.0%		Immune system disorder †	1.0%
	Temperature intolerance †	1.0%	Infections and infestations	Acute sinusitis †	1.0%
Injury, poisoning and procedural complications	Ankle fracture †	1.0%		Bacterial disease carrier †	1.0%
	Carotid artery restenosis †	1.0%		Bronchitis †	1.0%
	Fall †	4.1%		Candida infection †	2.1%
	Joint dislocation †	1.0%		Cellulitis †	2.0%
	Post procedural haematoma †	1.0%		Clostridium colitis †	1.0%
	Procedural pain †	1.0%		Conjunctivitis †	1.0%
	Procedural vomiting †	1.0%		Cystitis †	1.0%
	Pseudomeningocele †	1.0%		Endocarditis †	2.0%
	Subdural haematoma †	1.0%		Epididymitis †	1.0%
	Tracheal injury †	1.0%		Escherichia sepsis †	1.0%
	Vascular pseudoaneurysm †	1.0%		Fungal infection †	1.0%
Investigations	Biopsy salivary gland †	1.0%		Fungal skin infection †	1.0%
	Blood creatine phosphokinase increased †	2.0%		Gastroenteritis †	1.0%
	Blood creatinine increased †	1.0%		Genital infection fungal †	1.0%
	Blood glucose increased †	1.0%		Hand-foot-and-mouth disease †	1.0%
	Blood magnesium abnormal †	1.0%		Herpes zoster †	1.0%
	Blood pressure increased †	8.2%		Oral candidiasis †	4.1%
	Blood urea increased †	1.0%		Parotitis †	1.0%
	Cardiac enzymes increased †	1.0%		Pneumonia †	8.2%
	Electrocardiogram ST segment abnormal †	1.0%		Respiratory syncytial virus infection †	1.0%
	Electrocardiogram ST segment depression †	1.0%		Respiratory tract infection †	2.0%
	Glycosylated haemoglobin increased †	1.0%		Rhinitis †	1.0%
	Transaminases increased †	2.1%		Sepsis †	3.1%
	Troponin increased †	2.0%		Septic shock †	1.0%
	Urine output decreased †	1.0%		Sinusitis †	1.0%
	Weight decreased †	1.0%		Skin candida †	1.0%

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Less Common Adverse Events (1% to 20%)					
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**Upper limit reported (%)**
Metabolism and nutrition disorders	Decreased appetite †	1.0%	Infections and infestations	Wound infection †	1.0%
	Dehydration †	2.1%	Musculoskeletal and connective tissue disorders	Arthralgia †	5.2%
	Diabetes mellitus †	3.1%		Arthritis †	1.0%
	Dyslipidaemia †	2.0%		Back pain †	3.1%
	Electrolyte imbalance †	17.0%		Groin pain †	2.1%
	Fluid retention †	1.0%		Joint swelling †	1.0%
	Glucose tolerance impaired †	1.0%		Muscle spasms †	1.0%
	Gout †	1.0%		Musculoskeletal chest pain †	1.0%
	Hypercholesterolaemia †	3.1%		Musculoskeletal pain †	3.1%
	Hyperglycaemia †	9.1%		Neck pain †	1.0%
	Hyperlipidaemia †	2.0%		Osteoarthritis †	1.0%
	Hypernatraemia †	2.0%		Pain in extremity †	5.7%
	Hypervolaemia †	2.1%	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Appendix cancer †	1.0%
	Hypocalcaemia †	3.1%		Gastric cancer †	1.0%
	Hypokalaemia †	18.4%		Haemangioma of liver †	1.0%
	Hypomagnesaemia †	5.1%		Pancreatic carcinoma metastatic †	1.0%
	Hyponatraemia †	3.1%	Nervous system disorders	Amnesia †	1.0%
	Hypophosphataemia †	3.1%		Brain oedema †	4.5%
	Hypoproteinaemia †	1.0%		Carotid artery dissection †	1.0%
	Malnutrition †	3.1%		Carotid artery thrombosis †	1.0%
	Vitamin D deficiency †	1.0%		Cerebral artery embolism †	1.0%
Psychiatric disorders	Acute psychosis †	1.0%		Cerebral haemorrhage †	2.1%
	Agitation †	8.2%		Cerebral vasoconstriction †	12.2%
	Alcohol withdrawal syndrome †	1.0%		Complex regional pain syndrome †	2.1%
	Anxiety †	4.1%		Convulsion †	6.2%
	Confusional state †	1.0%		Dizziness †	2.0%
	Depressed mood †	1.0%		Encephalopathy †	1.0%
	Depression †	15.5%		Headache †	17.3%
	Depressive symptom †	1.0%		Hemianopia †	1.0%
	Insomnia †	9.2%		Horner's syndrome †	1.0%
	Mental status changes †	1.0%		Hydrocephalus †	1.0%
	Restlessness †	1.0%		Hypertonia †	1.0%
	Sleep disorder †	1.0%		ICH - HI -1 †	8.0%
	Stress †	1.0%		ICH - PH1 †	4.5%
Renal and urinary disorders	Azotaemia †	1.0%		Intracranial aneurysm †	2.0%
	Dysuria †	1.0%		Intracranial pressure increased †	2.1%
	Haematuria †	6.8%		Intraventricular haemorrhage †	4.1%
	Hypertonic bladder †	1.0%		Ischaemic stroke †	9.3%
	Oliguria †	1.0%		Lethargy †	1.0%
	Polyuria †	1.0%		Migraine †	1.0%
	Renal failure acute †	5.1%		Monoparesis †	1.0%
	Renal failure †	1.0%		Muscle spasticity †	2.1%
	Renal infarct †	1.0%		Neuralgia †	1.0%
	Renal mass †	1.0%		Paraesthesia †	1.0%
	Urethral pain †	1.0%		Partial seizures †	1.0%
	Urge incontinence †	1.0%		Presyncope †	1.0%
	Urinary retention †	9.2%			

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Less Common Adverse Events (1% to 20%)					
MedDRA System Organ Class	**MedDRA Preferred Term**	**Upper limit reported (%)**	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**Upper limit reported (%)**
Reproductive system and breast disorders	Benign prostatic hyperplasia †	4.1%	Nervous system disorders	Somnolence †	1.0%
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure †	3.4%		Status epilepticus †	1.0%
	Aspiration †	1.0%		Stroke in evolution †	8.2%
	Atelectasis †	3.1%		Subarachnoid haemorrhage †	1.1%
	Chronic obstructive pulmonary disease †	2.1%		Syncope †	2.1%
	Cough †	1.0%		Transient ischaemic attack †	1.0%
	Dyspnoea †	2.0%		Tremor †	2.1%
	Epistaxis †	1.0%		Vasculitis cerebral †	1.0%
	Haemoptysis †	1.0%	Skin and subcutaneous tissue disorders	Decubitus ulcer †	6.1%
	Hiccups †	2.1%		Dermatitis contact †	1.0%
	Hypoxia †	2.0%		Dermatitis †	1.0%
	Oropharyngeal pain †	1.0%		Ecchymosis †	2.1%
	Pleural effusion †	4.1%		Erythema †	3.1%
	Pneumonia aspiration †	10.2%		Intertrigo †	1.0%
	Pulmonary congestion †	1.0%		Pruritus †	2.1%
	Pulmonary embolism †	1.0%		Rash erythematous †	1.0%
	Pulmonary oedema †	4.5%		Rash †	2.0%
	Respiratory arrest †	1.0%		Skin lesion †	1.0%
	Respiratory distress †	4.1%	Surgical and medical procedures	Gastrostomy tube removal †	1.0%
	Respiratory failure †	4.1%	Vascular disorders	Aortic aneurysm †	1.0%
	Sleep apnoea syndrome †	1.0%		Arterial rupture †	1.0%
	Wheezing †	1.0%		Deep vein thrombosis †	10.2%
				Embolism arterial †	1.0%
				Femoral artery embolism †	1.0%
				Haematoma †	2.0%
				Hypertension †	5.1%
				Hypotension †	6.2%
				Lymphoedema †	1.0%
				Peripheral artery thrombosis †	1.0%
				Phlebitis superficial †	1.0%
				Phlebitis †	1.0%
				Thrombophlebitis †	3.1%
				Thrombosis †	1.0%
				Vascular occlusion †	1.0%
				Vasospasm †	3.1%
† Events were collected by systematic assessment					

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