Post-Market **R**egistry **O**f **S**troke **P**atients treated with Medtronic Neuro Thrombectomy Devices to collect **R**eal world data in **S**outh **E**ast **A**sia (PROSPR-SEA)

NCT03364023

Clinical Investigation Plan
Version A (13-MAR-2017)

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	**P**ost-Market **R**egistry **O**f **S**troke **P**atients treated with Medtronic Neuro Thrombectomy Devices to collect **R**eal world data in **S**outh **E**ast **A**sia (PROSPR-SEA)
Clinical Investigation Plan Identifier	MDT16066SOLSEA
Study Product Name	Medtronic Market-released Neurothrombectomy Devices
Sponsor/Local Sponsor	Medtronic Neurovascular 9775 Toledo way Irvine, CA 92618 Covidien Private Limited 50 Pasir Panjang Road Mapletree Business City #0451, Singapore 117384
Contract Research Organization (CRO)	[redacted]
Document Version	A (13-MAR-2017)
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Confidentiality Statement

1. Investigator Statement

Study product Name	Medtronic Market-released Neurothrombectomy Devices
Sponsor	Medtronic Neurovascular
Clinical Investigation Plan Identifier	MDT16066SOLSEA
Version Number/Date	A (13-MAR-2017)

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the Clinical Investigational Plan, GCPs, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IEC. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
Acute Ischemic Stroke (AIS)	Focal symptoms due to cerebral infarction from an arterial occlusion.
Alberta Stroke Program Early CT Score (ASPECTS)	A 10-point quantitative topographic CT scan score developed to offer the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes on the pretreatment CT studies in patients with acute ischemic stroke of the anterior circulation.
Product Complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device that has been released for distribution and placed in the market. (ASEAN-COM-01: Customer Complaint Handling)
Completed Subject	A study participant who has completed all study visits as outlined in the protocol.
Electronic Case Report Form (eCRF)	An electronic document designed to record all of the protocol requested information to be reported to the sponsor on each study subject. eCRFs are “living documents” in the respect that new information on the subject is continually gathered throughout the study.
Emboli in New Territory (ENT)	Embolization to territories outside of the target downstream territory.
Independent Ethics Committee (IEC)	Independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. (ISO 14155:2011 3.18).
Index Procedure	Very first stroke procedure involving treatment with a Medtronic market-released neurothrombectomy device.
Informed Consent Process	Process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation. NOTE Informed consent is documented by means of a written, signed and dated informed consent form. (ISO 14155:2011 3.21).
International Organization for Standardization (ISO)	International standard-setting body composed of representatives fromvarious national standards organizations.

Term	Definition
Investigator	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. (ISO 14155:2011 3.24). For the purposes of the protocol, 'Investigator' also refers to the Principal Investigator.
Modified Rankin Scale (mRS)	Commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other cause of neurological disability. It has become widely used in clinical outcome measures for stroke clinical trials. Scale for measuring general neurologic function: 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead
National Institutes of Health Stroke Scale (NIHSS)	Method for quantifying neurological deficits developed by the National Institutes of Health. It is used to assess the severity of a stroke.
Neurological Death	Death due to neurological cause
Principal Investigator	Qualified person responsible for conducting the clinical investigation at an investigation site. (ISO 14155:2011 3.33).
Screen Fail	Subject who sign the Informed Consent form and is identified later as failing to meet all inclusion/exclusion criteria.
Sponsor	A person who initiates a clinical investigation, but who does not actually conduct the Investigation, i.e., the test article is administered or

Term	Definition
	dispensed to or used involving, a subject under the immediate direction of another individual.
Symptomatic intracranial hemorrhage (sICH)	≥ 4 points worsening from baseline on the NIHSS scale associated with an image finding of intra-cranial hemorrhage (i.e., intracerebral or intraventricular) at 24 +/- 8 hrs post procedure.
Modified Thrombolysis in Cerebral Infarction (TICI) score	Scale to measure reperfusion. Grade 0 No Perfusion. No antegrade flow beyond the point of occlusion Grade 1 Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion Grade 2a Perfusion of less than half of the vascular distribution of the occluded artery (e.g. filling and perfusion through 1 M2 division) Grade 2b Perfusion of half or greater of the vascular distribution of the occluded artery (e.g. filling and perfusion through 2 or more M2 divisions) Grade 3 Full perfusion with filling of all distal branches

3. Synopsis

Title	**P**ost-Market **R**egistry **O**f **S**troke **P**atients treated with Medtronic Neuro Thrombectomy Devices to collect **R**eal world data in **S**outh **E**ast **A**sia (PROSPR-SEA)
Sponsor	Medtronic Neurovascular
Local Sponsor	Covidien Private Limited 50 Pasir Panjang Road Mapletree Business City #0451, Singapore 117384
Investigation Purpose	A post-market registry designed to collect real world data associated with the use of Medtronic market-released neurothrombectomy devices in acute ischemic stroke (AIS) patients from countries in South East Asia.
Clinical Study Type	Post Market Observation Study
Product Status	Market-released in Singapore, Thailand and Vietnam
Primary Objective	The primary objective of this registry is to assess clinical outcomes associated with the use of Medtronic market-released neurothrombectomy devices intended to restore blood flow in patients experiencing acute ischemic stroke due to large intracranial vessel occlusion within 8 hours of symptom onset.
Primary Endpoint	• Modified Rankin Scale (mRS) at 90 days
Secondary Objective	The secondary objective of this registry is to evaluate safety outcomes and collect real world data observed during standard of care stroke management practice associated with the use of Medtronic market-released neurothrombectomy devices.
Safety Evaluations	• Incidence of symptomatic Intracranial hemorrhage (sICH) at 24 hrs ± 8 hrs post procedure • All-cause mortality through 90 days post procedure • Incidence of emboli in new territory (ENT) at 24 hrs ± 8 hrs post procedure
Additional Evaluations	• Revascularization at the end of the procedure using mTICI score (0, 1, 2a, 2b, 3)

	• Workflow metrics (e.g., time from onset to door, time from door to imaging, time from imaging to puncture, time from door to revascularization, etc.) • Post-acute discharge disposition: discharge to home or any other type of facility (e.g. rehabilitation services, nursing facilities, hospice, etc.) • National Institutes of Health Stroke Scale (NIHSS) score at hospital discharge or ≤ 7 days post index stroke procedure, whichever comes first. • Subject disposition at study exit
Study Design	Prospective, multi-center, non-randomized, observational registry evaluating the use of Medtronic market-released neurothrombectomy devices in patients diagnosed with an acute ischemic stroke due to large intracranial vessel occlusion.
Sample Size	Up to 500 subjects from up to 15 sites in Singapore, Thailand and Vietnam
Inclusion/Exclusion Criteria	Inclusion Criteria 1. Subject/subject's legally authorized representative has given Informed Consent according to country regulations, and/or EC requirements. 2. Subject has experienced an Acute Ischemic Stroke due to large intracranial vessel occlusion in at least one of the following intracranial vessels: internal carotid artery (ICA), M1and M2 segments of the middle cerebral artery (MCA), basilar, and vertebral arteries. 3. Subject has been or will be treated with a Medtronic market-released neurothrombectomy device as the initial device used to remove the thrombus. 4. Subject is willing to participate in a 90-day follow-up visit. 5. Treatment within 8 hours of stroke symptom onset (defined as stroke onset to access puncture). Exclusion Criteria 1. Concurrent participation in another mechanical neurothrombectomy device trial or any other clinical trial with an active treatment arm or where the study procedure or treatment might confound the study analysis.
Study Procedures and Assessments	Assessments and stroke management procedures for stroke will be performed in this registry as per standard of care.

	Enrollment				Follow-up
Visit	**Baseline**	**Procedure**	**24 hrs Post Procedure**	**≤ 7 days or Discharge**	**90-Day**
Range	--	0	± 8 hrs	--	± 15 days
Day	0	0	1	7-10	90
Method	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit or Phone
Demographics and Medical History	◆				
mRS Assessment	◆[1]			◆	◆
NIHSS Assessment	◆[2]		◆[4]	◆	◆[6]
ASPECTS	◆[3]				
Mechanical Thrombectomy		◆[5]			
Adverse Event		◆	◆	◆	◆
Discharge Disposition				◆	

1. Pre-stroke mRS is completed at baseline by obtaining verification from an individual aware of the subject's functional status prior to stroke (e.g., family member, friend, etc.), as per standard of care. Pre-stroke mRS should reflect the subject's condition just prior to stroke onset. For example, if the subject was hospitalized during stroke onset, the subject's reason for hospitalization should be taken into account when evaluating the subject's pre-stroke mRS.
2. Pre-treatment NIHSS closest to start of procedure, as per standard of care.
3. ASPECTS evaluated from baseline imaging at enrolling hospital, as per standard of care.
4. Post-procedure NIHSS should reflect the latest score within the 24 ± 8 hour post procedure window, as per standard of care.
5. Required for subject to be eligible for the study.
6. Assessment will not be performed if visit is completed via phone

Subjects may be enrolled in this registry from the point of arrival at the enrolling hospital where treatment for their index stroke with a Medtronic market-released neurothrombectomy device has occurred, up to the day of hospital discharge or ≤ 7 days post index stroke procedure, whichever comes first. At discharge, the subject's disposition will be collected. Clinical outcomes will be assessed at 90 days post procedure (± 15 Days).

	A subject's participation in this prospective data collection registry will conclude at the completion of the 90-day follow-up.
Statistics	Study outcomes will be summarized descriptively and standard summary statistics will be calculated for all study variables, including means, standard deviations, medians and ranges for continuous variables and frequency distributions for categorical variables. The study's primary and safety assessments will be summarized and reported for the overall study cohort and in subgroups of interest.

4. Introduction

4.1. Background

Stroke is a devastating and debilitating disease. It is the second leading cause of death worldwide with rates higher in Asia than in Europe or North America and a leading cause of disability globally.[1,2] Annually, 15 million people experience a stroke worldwide of which, approximately 9 million are of the Asian population.[3] As the largest and most populated continent in the world, Asia accounts for more than half of the global population and nearly two-thirds of the overall global incidence of stroke with a higher proportion of these incidences being ischemic strokes.[4]

The most devastating ischemic strokes are those caused by large-vessel occlusions as they carry a high burden of morbidity and mortality.[5-9] Clinical evidence has demonstrated that effective recanalization of these large vessels is strongly associated with improved functional outcomes.[10-17] In fact, successful recanalization is associated with a 4- to 5-fold increase in the odds of good final functional outcome and a 4-to 5-fold reduction in the odds of death.[12] In addition, robust clinical evidence has established that good functional outcome (e.g. modified Rankin Scale (mRS) score 0-2) following successful recanalization is significantly time-dependent. Results from five randomized trials consisting of 634 patients assigned to the endovascular thrombectomy and medical therapy arm demonstrated that earlier treatment was associated with a substantially lower degree of patient disability at 3 months.[18] The data from the pooled analysis showed that every 9-minute delay in symptom onset–to–substantial endovascular reperfusion time, 1 of every 100 treated patients had a worse disability outcome (higher score by 1 or more levels on the mRS).[18] Therefore, immediate therapeutic intervention is critical because a delay in treatment significantly reduces the probability of good clinical outcomes for the patient.

Given that time to reperfusion is a critical factor in achieving good clinical outcomes, efforts to increase efficiency and minimize delays in the early management of acute ischemic stroke patients are essential and have been acknowledged. For example, the American Heart/Stroke Associations have set a guideline of a targeted time of patient arrival to the hospital facility to IV t-PA administration (door-to-needle time) of ≤ 60 minutes.[19] In addition, the establishment of primary stroke centers or comprehensive stroke centers has helped to reach shorter door-to-needle times.[19,20] Additional efforts have also been made to achieve swift door-to-needle times in order to more rapidly restore blood flow to the affected vessel and brain tissue with emergent intra-arterial therapy (direct aspiration devices and stent retrievers).[21]

Neurothrombectomy devices, such as stent retrievers, are commercially available on the market to treat acute ischemic stroke caused by large-vessel occlusions. Recently published data from five randomized controlled studies consistently shown that endovascular clot retrieval with stent retrievers in addition to best medical treatment (± IV t-PA) improves outcome in acute anterior circulation stroke patients with

proximal vessel occlusion.[22-26] However in these studies, only three subjects were enrolled from one participating Asian country. Thus, studies and clinical data specific to Asia are still limited.

With the incidence of stroke continually increasing in developing countries in Asia, empirical evidence from real world data collection will provide a better understanding of the current stroke situation in South East Asia.

4.2. Purpose

PROSPR-SEA is a post-market registry designed to collect real world data associated with the use of Medtronic market-released neurothrombectomy devices in acute ischemic stroke (AIS) patients from countries in South East Asia. The primary objective of this registry is to assess clinical outcomes associated with the use of these devices in patients experiencing AIS due to large intracranial vessel occlusion within 8 hours of symptom onset.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this registry is to assess clinical outcomes associated with the use of Medtronic market-released neurothrombectomy devices intended to restore blood flow in patients experiencing acute ischemic stroke due to large intracranial vessel occlusion within 8 hours of symptom onset.

5.1.1.1. Primary Endpoint

The following will be assessed:

- Modified Rankin Scale (mRS) at 90 days.

5.1.2. Secondary Objective(s)

The secondary objective of this registry is to evaluate safety outcomes and collect real world data observed during standard of care stroke management practice associated with the use of Medtronic market-released neurothrombectomy devices.

5.1.2.1. Safety Evaluations

The following events will be reported and evaluated:

- Incidence of symptomatic Intracranial hemorrhage (sICH) at 24 hrs ± 8 hrs post procedure
  - sICH: ≥ 4 points worsening from baseline on the NIHSS scale associated with an image finding of intra-cranial hemorrhage (i.e. intracerebral or intraventricular) at 24 ± 8 hrs post procedure.
- All-cause mortality through 90 days post procedure
- Incidence of emboli in new territory (ENT) at 24 hrs ± 8 hrs post procedure
  - ENT: Embolization territories outside of the target downstream territory

5.1.2.2. Additional Evaluations

The following additional assessments for evaluation will be completed:

- Revascularization at the end of the procedure using mTICI score (0, 1, 2a, 2b, 3)
- Workflow metrics (e.g., time from onset to door, time from door to imaging, time from imaging to puncture, time from door to revascularization, etc.)
- Post-acute discharge disposition: discharge to home or any other type of facility (e.g. rehabilitation services, nursing facilities, hospice, etc.)
- National Institutes of Health Stroke Scale (NIHSS) score at hospital discharge or ≤ 7 days post index stroke procedure, whichever comes first.
- Subject disposition at study exit

6. Study Design

This is a prospective, multi-center, non-randomized, observational registry of AIS patients that have or will undergo treatment with the use of a Medtronic market-released neurothrombectomy device (as the initial device used to remove the thrombus) within 8 hours of stroke symptom onset. This registry aims to collect real world data on patients in whom the decision of device use has been made prior to data collection. This registry does not aim to affect patient care, but rather only to document outcomes observed during standard of care stroke management practice at investigation sites.

Methods incorporate to minimize bias were considered and up to 500 subjects will be enrolled at up to 15 sites in Singapore, Thailand and Vietnam. Each site is expected to enroll a minimum of 10 subjects, not to exceed a maximum of 75 subjects per site to ensure wide spread distribution of data. Sponsor approval must be obtained prior enrolling additional subjects.

All study clinicians and Medtronic/study personnel will be trained on the corresponding aspects of the study using standardized training materials and required to follow the CIP. Subjects may be enrolled in this registry from the point of arrival at the enrolling hospital where treatment with a Medtronic market-released neurothrombectomy device is to occur, up to the day of hospital discharge, or ≤ 7 days after index stroke procedure, whichever comes first. The baseline through discharge visits will take place

at the treating hospital. Subject's participation in this prospective data collection registry will conclude at the completion of the 90-day follow-up.

An overview of the registry flow is depicted in Figure 1.

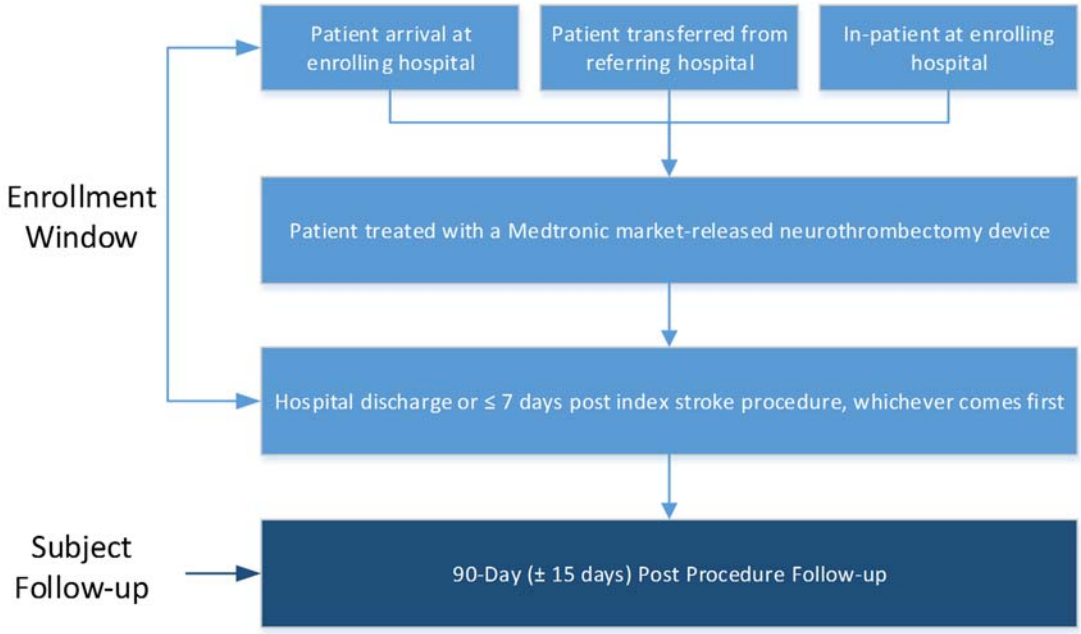

Figure 1. Registry Flowchart

6.1. Duration

Patients who are treated with a Medtronic marked-released neurothrombectomy device and who meet the Inclusion/Exclusion criteria may be enrolled over a period of 24 months with a 90-day follow-up period. The total duration of the registry will be approximately 36 months.

6.2. Rationale

Advancements in technology have led to improvements in the treatment of patients with acute ischemic stroke due to large vessel occlusion. Based on the recently published results from five randomized controlled trials, the American Heart Association/American Stroke Association updated the guidelines to strongly recommend endovascular treatment with stent retrievers in addition to intravenous thrombolysis.[27] Patient-level pooled analysis of the five trials showed that 46% of patients treated with mechanical thrombectomy achieved functional independence (mRS 0-2) at 90 days.[28] Though patients are being treated with mechanical thrombectomy worldwide, there is still a lack of studies and data

available to evaluate the stroke population that is currently being treated in South East Asia. Thus, it is evident that further establishment of robust clinical evidence is necessary as it facilitates treatment decisions by physicians and caregivers, impacts healthcare coverage, and drives clinical practice guidelines. The use of clinical data collected from real-world market released neurothrombectomy devices used for AIS patients is important as it builds upon the clinical evidence necessary to support the practice of evidence-based medicine.

PROSPR-SEA will assess the clinical outcomes associated with the use of Medtronic market-released neurothrombectomy device in acute ischemic stroke patients from countries in South East Asia including, Vietnam, Thailand and Singapore. As an area that is most affected by rising prevalence of stroke, the real-world data that will be collected from this registry will provide a better understanding of stroke management in South East Asia.

7. Product Description

7.1. General

The products used in this registry are Medtronic market-released neurothrombectomy devices designed to restore blood flow in patients experiencing an AIS due to large intracranial vessel occlusion within 8 hours of stroke symptom onset. This is a prospective registry that intends to collect real world data on subjects in whom the decision of device use has been made prior to data collection.

The Medtronic neurothrombectomy devices used in this registry are commercially available and used within intended use in the involved participating countries. **Table 1** shows the available models with product specification and recommended sizing guide. All models may not be commercially available in every country participating in this registry; each study center is to use only the commercially available models in their country. These devices will not be supplied by the Sponsor for purposes of this registry.

Additional device information such as indication for use, description, procedure, and operating information is described in detail in the Instructions for Use (IFU).

Table 1. Solitaire™ Device Models - Product Specification and Recommended Sizing Guide

Model	Recommended Vessel Diameter (mm)		Minimum Microcatheter ID		Push Wire Length	Radiopaque Markers	
	Min.	Max.	(mm)	(in)	(cm)	Distal	Prox.
SRD-4-15 **SFR-4-15** **SFR2-4-15**	2.0	4.0	0.5	0.021	180	3	1
SRD-4-20 **SFR-4-20** **SFR2-4-20** **SFR3-4-20-10**	2.0	4.0	0.5	0.021	180	3	1
SFR2-4-40 **SFR3-4-40-10**	2.0	4.0	0.5	0.021	180	3	1
SRD-6-20 **SFR-6-20** **SFR2-6-20** **SFR3-6-20-10**	3.0	5.5	0.7	0.027	180	4	1
SRD-6-30 **SFR-6-30** **SFR2-6-30**	3.0	5.5	0.7	0.027	180	4	1

8. Selection of Subjects

8.1. Study Population

The registry population consists of subjects that have suffered an AIS due to large intracranial vessel occlusion who are treated with a Medtronic market-released neurothrombectomy device within 8 hours of stroke symptom onset.

8.2. Subject Enrollment

Up to 500 subjects will be enrolled in this registry from up to 15 sites in Singapore, Thailand and Vietnam.

Subjects may be enrolled in this registry from the point of arrival at the enrolling hospital for treatment of their index stroke with a Medtronic market-released neurothrombectomy device, up to the day of hospital discharge or ≤7 days post index procedure, whichever comes first. The day of discharge is considered to be the date the subject is initially discharged from the acute hospital to home, rehab (even within same facility), etc. A subject is considered enrolled when informed consent is obtained and the subject has satisfied all eligibility criteria.

8.3. Inclusion Criteria

1. Subject/subject's legally authorized representative has given Informed Consent according to country regulations, and/or EC requirements.
2. Subject has experienced an Acute Ischemic Stroke due to large intracranial vessel occlusion in at least one of the following intracranial vessels: internal carotid artery (ICA), M1 and M2 segments of the middle cerebral artery (MCA), basilar, and vertebral arteries.
3. Subject has been or will be treated with a Medtronic market-released neurothrombectomy device as the initial device used to remove the thrombus.
4. Subject is willing to participate in a 90-day follow-up.
5. Treatment within 8 hours of stroke symptom onset (defined as stroke onset to access puncture).

8.4. Exclusion Criteria

1. Concurrent participation in another mechanical neurothrombectomy device trial or any other clinical trial with an active treatment arm or where the study procedure or treatment might confound the study analysis.

9. Study Procedures

9.1. Schedule of Events

Assessments and procedures for stroke management will be performed in this registry as per standard of care. Subjects enrolled into the registry will follow the schedule of assessments to be performed at each study visit as listed in the **Table 2**.

Table 2. Visit and Assessment Schedule

	Enrollment				Follow-up
Visit	**Baseline**	**Procedure**	**24 hrs Post Procedure**	**≤ 7 days or Discharge**	**90-Day**
Range	--	--	± 8 hrs	--	± 15 days
Day	0	0	1	7-10	90
Method	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit or Phone
Demographics and Medical History	◆				
mRS Assessment	◆[1]			◆	◆
NIHSS Assessment	◆[2]		◆[4]	◆	◆[6]
ASPECTS	◆[3]				
Mechanical Thrombectomy		◆[5]			
Adverse Events		◆	◆	◆	◆
Discharge Disposition				◆	

1. Pre-stroke mRS is completed at baseline by obtaining verification from an individual aware of the subject's functional status prior to stroke (e.g., family member, friend, etc.), as per standard of care. Pre-stroke mRS should reflect the subject's condition just prior to stroke onset. For example, if the subject was hospitalized during stroke onset, the subject's reason for hospitalization should be taken into account when evaluating the subject's pre-stroke mRS.
2. Pre-treatment NIHSS closest to start of procedure, as per standard of care.
3. ASPECTS evaluated from baseline imaging at enrolling hospital, as per standard of care.
4. Post-procedure NIHSS should reflect the latest score within the 24 ± 8 hour post procedure window, as per standard of care.
5. Required for subject to be eligible for the study.
6. Assessment will not be performed if visit is completed via phone

90-day Follow-up

The 90-day follow-up will be conducted as an office visit or via phone by the Investigator or research staff to collect information related to the subject's mRS and overall clinical condition. If the subject is unavailable for any reason, the subject's family/relative or caregiver/ legally authorized representative will be requested to provide the applicable information. A subject's participation in this prospective data collection registry will conclude at the completion of the 90-day follow-up. A follow-up electronic case report form (eCRF) will be completed for every subject that is enrolled into this registry, including subjects who prematurely discontinue.

9.2. Subject Screening

Given that the prospective study population consists of patients who have or will undergo treatment with the use of a Medtronic market-released neurothrombectomy device and that the screening assessments consist of standard patient diagnostics for this therapy, subjects are considered enrolled in the study once the subject has signed and dated the informed consent. If the subject signs the Informed Consent form and is identified later as failing to meet all eligibility criteria, the subject will be classified as a screen failure. Upon determination that the subject does not qualify for enrollment, the reason for the subject's screen failure status will be documented on a Screening and Enrollment Log, in order to minimize bias. No eCRFs in the Electronic Data Capture (EDC) system are required to be completed for screen failure subjects.

9.3. Medical History

Relevant stroke related medical conditions listed in the eCRFs that present prior to the Medtronic market -released neurothrombectomy device procedure (i.e., from subject's arrival at the enrolling hospital through the index procedure), should be documented under medical history.

9.4. Subject Consent

The Principal Investigator or his/her authorized designee will conduct the informed consent process and ensure the nature and objective of this registry is thoroughly explained to the subject and/or subject's legally authorized representative (LAR) in the language understood by the subject/subject's LAR. The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject. Language used should be non-technical and should not waive or appear to waive the subject's legal rights. The consent process can occur at any point during the enrollment period (from the point of arrival at the enrolling hospital where treatment for their index stroke with a Medtronic market-released neurothrombectomy device has occurred, up to the day of hospital discharge or ≤ 7 days post index stroke procedure, whichever comes first). The consent process will be done according to country regulations and/or IEC.

The Principal Investigator is responsible for ensuring informed consent form (ICF) is obtained from each subject and/or subject's LAR prior to subject enrollment and entering of any subject data into the registry database. Informed consent must be documented prior to any procedure specific to the clinical study is applied to the subject.

The ICF is required and must be obtained in a format approved by the IEC. The form should contain standard language consistent with local policies for ensuring privacy of confidential information. The ICF must be reviewed and approved by the Sponsor prior to submission to the appropriate IEC for approval.

The Investigator is responsible for ensuring any new information related to the registry will be provided to the subject and/or subject's LAR, if applicable. Subject may need to be re-consented to continue participation in the registry, as required by country regulations and/or IEC.

After all persons have signed and dated the informed consent form, the investigator must provide the subject with a copy of the signed and dated informed consent form.

9.5. Assessment of Safety

Assessment of safety shall be based on the following:

- Incidence of symptomatic Intracranial hemorrhage (sICH) at 24 hrs ± 8 hrs post procedure
  - sICH: ≥ 4 points worsening from baseline on the NIHSS scale associated with an image finding of intra-cranial hemorrhage (i.e. intracerebral or intraventricular) at 24 ± 8 hrs post procedure.
- All-cause mortality through 90 days post procedure
- Incidence of emboli in new territory (ENT) at 24 hrs ± 8 hrs post procedure
  - ENT: Embolization territories outside of the target downstream territory

9.6. Recording Data

Study data will be collected using eCRFs and stored in a validated, password protected electronic data capture (EDC) system. The system allows the capability of data collection remotely through the internet so the participating investigation site personnel may log on to the system securely and enter the data. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical meaningfulness. Data entered on eCRFs will be derived from source documents, which may include worksheets and patient medical records. Periodic review of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

The Principal Investigator is responsible for reviewing all eCRF entries for completion and correctness. Changes in case report forms will be made electronically and the system used will keep an audit trail of changes. If necessary, an explanation for the change(s) may be provided. The Principal Investigator will electronically approve all eCRF data.

All study staff that enter data into eCRFs will undergo appropriate training for use of eCRFs. Further information regarding eCRF navigation and use may be found in the eCRF Completion Guidelines.

9.7. Deviation Handling

This registry is designed for the collection of real-world data for acute ischemic stroke patients treated with Medtronic market-released neurothrombectomy devices in the clinical setting. The clinical investigational plan (CIP) does not mandate specific care or visits not considered standard of care at the treating hospital and therefore would not be considered a protocol deviation if not completed.

A CIP deviation must be reported for the following situation:

- Failure to properly obtain informed consent per GCP, IEC and/or local institutional policies
- Failure to report SAEs within the reporting timelines as described in **Section 11.2**
- Failure to complete protocol training prior to performing study related activities

All deviations shall be entered as soon as possible in the electronic data capture system. Protocol deviations will be routinely reviewed by the Sponsor's study team. Where deviations occur, investigation sites are expected to implement corrective actions to prevent reoccurrence. Investigation sites with a high rate of protocol deviations will be closely monitored. If an investigation site demonstrates lack of compliance with the protocol and continuous protocol deviations are noted, the clinical site may be suspended from enrolling additional subjects or terminated from the study at the Sponsor's discretion.

9.8. Subject Withdrawal or Discontinuation

All enrolled subjects have the right to withdraw their consent at any time during the registry without penalty or loss of medical care. Whenever possible, the research staff should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. If the research staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record.

Subjects may also be withdrawn from the registry at any time at the discretion of the Investigator with or without the subject's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject. If a subject is withdrawn from the study, the Investigator will promptly inform the subject and Sponsor.

If a subject is withdrawn or discontinue their participation in the registry, the reason for withdrawal/discontinuation shall be recorded in the eCRF and in the subject's medical record. All data collected until the time of subject withdrawal/discontinuation will remain in the registry database and will be used for analysis.

9.9. Subject Lost to Follow-up

A subject will be considered lost to follow-up when efforts to reach the subject for the 90-day follow-up are unsuccessful. It is recommended that research staff document a minimum of two (2) attempts to reach the subject. All documentation should be retained in the subject binder.

10. Risks and Benefits

10.1. Potential Risks

Participation in a registry does involve the potential risks of a breach of confidentiality of medical record information and associated privacy of the participants. The Investigator will continuously monitor, assess, and document these risks and make all required efforts to ensure that patient information remains confidential as described in **Section 15.8**. There are no expected additional risks relative to the participation in this study as patients are treated according to general clinical practice and the Medtronic neurothrombectomy devices used are commercially available and used in accordance with the approved labeling. Therefore no risks other than the risk typically associated with the device and/or procedure, as indicated in the Instructions for Use, are anticipated.

10.2. Potential Benefits

There are no direct benefits or compensation to the subject resulting from their participation in this registry. However, information gained from the conduct of this registry may be of benefit to other persons with the same medical condition.

10.3. Risk-Benefit Rationale

As these patients will be or have been treated with a Medtronic market-approved Neurothrombectomy device as per standard of care, there is no additional physical risk, beyond what is included in the IFU, associated with the participation in this registry. Therefore the benefit of collecting real world data on a global level, which would assist in improving the treatment of AIS in the South East Asia region, outweigh the potential risks in the defined subject population.

11. Adverse Events and Post Market Surveillance

For the purpose of this real-world registry, the following Serious Adverse Events shall be collected:

- Symptomatic Intracranial Hemorrhage (sICH) at 24 ± 8 hrs post procedure
- Death through 90 days post procedure classified as neurological or non-neurological, with event leading to death.

All Medtronic devices/products (including regulatory approved components used in combination with the study product) used in this study are marked released. Therefore, Post Market Surveillance is applicable as described in **Section 11.3**.

11.1. Definitions/Classifications

11.1.1. Symptomatic Intracranial Hemorrhage (sICH) and Death

Table 3. Definition of sICH and Death

Symptomatic Intracranial Hemorrhage (sICH)	≥ 4 points worsening from baseline on the NIHSS scale associated with an image finding of intra-cranial hemorrhage (i.e., intracerebral or intraventricular) at 24 +/- 8 hrs post procedure..
Death (neurological or non-neurological)	Any subject death that may or may not be due to neurological reasons.

11.1.2. Causality Assessment

The relationship between the use of the:

- Study device (Medtronic market-released neurothrombectomy device) and
- The medical -surgical procedure (Procedure related events refers to the procedure related to the initial application of the Medtronic market-released neurothrombectomy device not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events).

The occurrence of each adverse event shall be assessed and categorized according to five different levels of causality for which the following definitions shall be used to assess the relationship of the adverse event to the investigational medical device or procedure:

1. Not Related:

   Relationship to the device or procedures can be excluded when:

   - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis*, when applicable [*If an investigational device gives an incorrect diagnosis, the subject might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the subject might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition];
- harms to the subject are not clearly due to use error;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2. Unlikely:

   The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3. Possible:

   The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4. Probable:

The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

5. Causal relationship:

   The adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:

   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that:
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on:
       - the adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
       - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
       - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
       - harm to the subject is due to error in use;
       - the event depends on a false result given by the investigational device used for diagnosis*, when applicable;
       - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Investigators shall distinguish between the adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation).

An adverse event can be related both to the procedure and the investigational device.

Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of investigational device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented.

The Investigators will make the maximum effort to define and categorize the event and avoid these situations.

11.1.3. Product Complaints

Product Complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device that has been released for distribution and placed in the market. (ASEAN-COM-01: Customer Complaint Handling)

11.2. Reporting of Adverse Events

For this study, the investigation site is only required to report to the Sponsor the Protocol defined SAEs, as specified in **Table 3.**

Investigators must obtain all information available to determine the start date, stop date, causality, action taken and outcome of the reported SAE and report immediately to the Sponsor not later than **24 hours** of being aware the event.

The investigator shall also send all requested supporting documentation (blinded/de-identified as to the subjects' identity) per the sponsor request.

The primary method of SAE reporting to the Sponsor will be through the electronic study database on the Adverse Event eCRF.

If the database is unavailable/not accessible the Investigator may email the information on the provided serious adverse event form to [redacted]. As soon as the database becomes available, the Investigator must complete data entry in the study database with the same information provided on the paper form.

A summary of site required expedited sponsor reporting requirements is detailed in **Table 4**.

Table 4. Site Required Expedited Sponsor Reporting Requirements

	Timeframe	Reporting Method
Symptomatic Intracranial Hemorrhage (sICH)	Immediately and not later than **24 hours** of awareness.	• Primary Method: **Adverse Event eCRF** • Secondary Method: [redacted]
Death		

The SAEs are required to be collected in the eCRF for all subjects starting from the point of groin puncture on the day of the study procedure (Day 0) through the subject's exit from the study (Day 90).

If a SAE is not resolved at the time of the 90-day follow-up, the SAE will be considered ongoing and no further action will be required by the Investigator for the registry.

Additionally, Investigator should assess whether the reported SAEs meets the criteria for expedited reporting to regulatory agency(ies) and IECs within the specified reporting timeframe, where applicable.

In some countries, regulatory agency(ies) and IECs may mandate additional collection of adverse events beyond the protocol defined SAEs reporting requirements mentioned in this section. It is the responsibility of the Principal Investigator and Sponsor, if applicable, to ensure these national and local regulations and requirements are met.

11.3. Post Market Surveillance

Devices/products (including regulatory approved components used in combination with an investigational product) used in this study are market released in Singapore, Vietnam and Thailand. Therefore, vigilance reporting is applicable.

The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements.

It is the responsibility of the investigator and the clinical study teams to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse. Reporting must be done immediately within 48 hours and via the regular channels for regulatory approved products. The reporting of product complaints by the clinical team

must be done according to the local SOP. Product complaints are categorized using the definition in **Section 11.1.3.**

12. Data Review Committees

A Steering Committee will oversee the conduct and scientific aspects of the study. A Steering Committee will be comprised of a minimum three (3) physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study will be responsible for providing expert medical guidance in the following roles:

- Advising on the study design and scientific value of data collection
- Monitoring the overall conduct and progress of the study
- Providing guidance to investigation sites

13. Statistical Design and Methods

13.1. Primary Analysis Cohort

All enrolled subjects treated with Medtronic market-released neurothrombectomy devices.

13.2. General Principles

The primary analysis for all baseline characteristics and study outcomes will include all enrolled subjects treated with Medtronic market-released neurothrombectomy devices. All available data will be included in primary study analyses. Standard summary statistics will be calculated for all study variables. For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized in frequency distributions. One-sided statistical tests will have p-values less than 0.025 deemed significant while two-sided tests will have p-values less than 0.05 deemed significant. All testing will be performed using a two-sided test at a 0.05 level of significance or a one-sided test at a 0.025 level of significance.

All statistical analyses will be performed using SAS (version 9.2 or higher, SAS Institute Inc. Cary, NC), R (version 3.0 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted and validated statistical or graphical software.

13.3. Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up, etc.) will be summarized with frequency tables.

13.4. Analysis of Objectives and Subgroups of Interest

For the primary study endpoint, the following will be measured:

- Modified Rankin Scale (mRS) at 90 days

For safety, the following evaluations will be made:

- Incidence of symptomatic Intracranial hemorrhage (sICH) at 24 hrs ± 8 hrs post procedure
  - sICH: ≥ 4 points worsening from baseline on the NIHSS scale associated with an image finding of intra-cranial hemorrhage (i.e. intracerebral or intraventricular) at 24 ± 8 hrs post procedure.
- All-cause mortality through 90 days post procedure
- Incidence of emboli in new territory (ENT) at 24 hrs ± 8 hrs post procedure
  - ENT: Embolization territories outside of the target downstream territory

The following will be measured as additional study evaluations:

- Revascularization assessment at the end of the procedure using mTICI score (0, 1, 2a, 2b, 3)
- Workflow metrics (e.g., time from onset to door, time from door to imaging, time from imaging to puncture, time from door to revascularization, etc.)
- National Institutes of Health Stroke Scale (NIHSS) score at hospital discharge
- Post-acute discharge disposition: discharge to home or any other type of facility (e.g. rehabilitation, nursing facilities, hospice, etc.)
- Subject disposition at study exit

All data will be summarized descriptively according to the general principles outlined above. Data from the present study may also be compared to or pooled with similar Medtronic investigations for the purposes of analysis and reporting.

13.5. Stratification of Population for Analysis and Sample Size

The overall study population will be sub grouped to assess trajectories of outcome in various cohorts of interest, including subgroups defined by NIHSS (to assess outcome by severity of stroke) and subgroups defined by discharge disposition (to assess the association between outcome and discharge status). Subgroups will be summarized separately from one another and from the overall cohort, and statistical comparisons among subgroups will be performed.

As study outcomes are prospectively intended to be summarized descriptively, sample size is not based on formal hypothesis testing and power calculations. The study sample size of 500 is expected to provide sufficient data to summarize overall results as well as outcomes within subgroups of interest and therefore there will be no. Each site is expected to enroll a minimum of 10 subjects, not to exceed a maximum number of 75 subjects that can included at each per site (15% of the total sample size), to ensure a sufficient global contribution.

13.6. Handling of Missing Data and Deviations

The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects deceased during study follow-up will be scored as mRS of 6 and will therefore be included in the analyses without the need for replacement of missing data. Other missing data will not routinely be replaced, and summaries and tabulations will be based on all available data as stated above.

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

14. Ethics

14.1. Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Ethics Committee (i.e., Ethics Board/Institutional Review Board (IRB)/Medical Ethics Committee (MEC)/Research Ethics Board (REB)) before initiating a study, continuing review of an ongoing study by an Ethics Committee, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

This study is not following ISO 14155:2011 standard in full extent.

The study is designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical study and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, contributing to, the clinical study. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical study.

In addition, this study will be conducted in compliance with applicable regional regulatory regulations and applicable laws of the countries where the study will be conducted, and if applicable, any additional requirements imposed by the IEC or regulatory authority.

The principles of the Declaration of Helsinki have been implemented through the patient informed consent (PIC) process, IEC approval (where applicable), study training, clinical trial registration, preclinical testing, risk-benefit assessment, publication policy etc.

14.1.1. Investigator Compliance

The Principal Investigator (PI) assumes full responsibility for performance of the research study in accordance with the CIP, Clinical Study Agreement, Investigator agreement, GCPs, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IEC. The PI shall be responsible for the day-to-day conduct of the clinical investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

14.1.2. Sponsor Compliance

The Sponsor is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the data generated are recorded and reported in accordance with established procedures. The study will be organized, and performed, in compliance CIP, Standard Operating Procedures, applicable regulations and recognized standards and any additional requirements imposed by the IEC, and regulatory authorities.

14.1.3. Independent Ethics Committee (IEC)

The Sponsor or representative of the Sponsor and/or Investigator must submit the CIP and subject ICF to the appropriate IEC. A site cannot participate in the registry and subjects cannot be enrolled until a copy of written and dated approval from IEC has been received by the Sponsor.

The date of the review the documents approved (e.g. CIP, ICF) should be clearly stated on the written IEC approval. In addition, the approval letter needs to be accompanied by an IEC roster, letter of compliance, or other documentation to allow verification that the Investigator, other investigation site personnel, and/or Sponsor personnel are not members of the IEC. If they are members of the IEC, written documentation is required stating that he/she did not participate in the approval process.

Any amendment or modification to the clinical protocol must be sent to the IEC. The IEC must also be informed of any event likely to affect the safety of subjects or the conduct of the study.

The IEC may impose any additional requirements (e.g. safety reports, progress reports etc.). The Sponsor will provide the Investigator any required documents for reporting to the IEC. Investigators must inform the Sponsor of any change in status of IEC approval. If any action is taken by an IEC with respect to the investigation, that information will be forwarded to the Sponsor by the respective Investigator.

A list of IECs including name, addresses, and chairpersons is maintained separately and regularly updated.

15. Study Administration

15.1. Study Contacts

A list of Study Contacts, including Name, title, address, and telephone number(s) of Sponsor Clinical Study Manager, Local Project Manager, Local Monitors and Medical/Safety contact will be sent to the site separately and maintained and regularly updated.

15.2. Site Selection

The Sponsor or a representative of the Sponsor will assess each potential site to ensure the Investigator and research staff has the facilities, qualifications, expertise, and ability to conduct the study in accordance to the CIP.

To participate, an investigation site should have the following:

- 24/7 stroke interventional capabilities
- 24 hour and discharge NIHSS should be routinely conducted as part of hospital's standard of care for all stroke patients receiving mechanical thrombectomy treatment, regardless of IV-tPA administration
- Ability to support quality and timely data collection via an Internet-based EDC system
- Resources for conducting the informed consent process
- Willingness to conduct 90-day follow-ups
- Willingness to sign and adhere to the study protocol and Investigator Agreement

A list of investigation sites including Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s) is maintained separately and regularly updated.

15.3. Site Initiation

The PI and research staff will be trained during the Site Initiation Visit (SIV). Investigator(s) and research staff who are unable to attend the SIV, must be trained by the Sponsor, Sponsor representative, or the fully trained PI and/or Primary Research Coordinator, prior to performing any study-related activities.

At a minimum, prior to subject enrollment, each site will provide the following documentation to the Sponsor:

- Signed Clinical Trial Agreement (CTA)
- Signed Investigator Agreement
- PI Curriculum Vitae (CV)
- IEC approval for the study

- IEC approved ICF for the study
- Ethics Board approval (and voting list, as required by local law) of the current version of the CIP and ICF
- Regulatory authority approval or notification (as required per local law)
- Training Log documentation to verify the appropriate research staff has been trained on the CIP and the conduct of the registry
- Completed Delegation of Authority (DOA) Log

The Sponsor will provide site with documentation of study center/investigator readiness. Evidence of center/investigator readiness must be received prior to subject enrollment and must be filed in the investigator site file (ISF).

15.4. Site Training

Each site will be trained on the CIP and any amendments, if applicable. Required training will be described in the study training plan. Investigator and research staff will undergo training prior to performing any study-related activities. All training must be documented.

15.5. Monitoring

Medtronic Neurovascular, as the Sponsor will be responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted in compliance with GCP. The Sponsor shall assess the extent and nature of monitoring appropriate for this study, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, and critical data points for evaluation.

Appropriately trained personnel appointed by Sponsor will conduct monitoring as per the Clinical Monitoring Plan. Monitors for the clinical study will consist of qualified staff from Clinical Research Organization (CRO) appointed by the Sponsor.

Study Monitors can conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed Investigator agreement, and compliance with IEC conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the Investigator and research staff is cause for the Sponsor to suspend/terminate the study at site or terminate the Investigator and research staff from the study participation. Frequency of monitoring may be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

15.5.1. Monitoring Reports

After each monitoring visit, the monitor will send to the PI an e-mail or letter summarizing the monitoring visit. A monitoring report summarizing any findings or action items, and also includes a summary of the meeting with the PI at the conclusion of the visit will be completed by the on-site monitor. The report will include the date of the monitoring visit, the site name, the name of the monitor, the name of the investigator, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. The PI will be responsible for ensuring that follow-up action items requiring resolution at the site are completed in an accurate and timely manner.

15.5.2. Close-out Visit

Final close out visits will be conducted at the end of the study, or earlier if applicable. The purpose of the final visit is to ensure all outstanding study data documents have been submitted to the sponsor, review record retention requirements with the PI and ensure that all applicable requirements are met for the study.

15.6. Data Management

Every effort will be made to ensure the accuracy and reliability of data including the selection of qualified Investigators and appropriate study centers, review of clinical protocol procedures with the Investigator and associated personnel before the study commences, and periodic monitoring visits by the Sponsor as deemed appropriate. Guidance for eCRF completion will be provided and reviewed with the study personnel prior to the start of the study. The Sponsor will review eCRFs for accuracy and completeness and any discrepancies will be resolved with the PI or designee, as appropriate.

The PI must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the Investigator, and filed in the subject medical file.

Only authorized persons listed on the Delegation of Authority (DOA) Log can complete/sign the eCRFs. eCRFs shall be signed by PI attesting to their review and agreement of the data collected.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in the eCRFs. If a person is only authorized to complete eCRFs or to make changes to an already signed eCRF, the PI shall re-sign this eCRF.

15.6.1. Data Quality Assurance

The EDC system selected by the Sponsor will support all data collection for this study. Documentation pertinent to the use of the EDC system will be made available for use by appropriate investigation site personnel. All individuals who will be expected to use the EDC system will be given adequate training necessary to perform their assigned tasks as described. Training will be conducted by qualified individuals initially and on a continuing basis, as needed.

15.6.2. Data Handling

The Sponsor is responsible for compilation and verification of the study data, retention of the clinical study database, performance of statistical analyses, and preparation of the study reports. The Sponsor will ensure that the performance of Data Management activities occur in accordance with the study Data Management Plan.

15.6.3. Data Ownership

Rights, duties, and obligations regarding ownership of any ideas, concepts, inventions, or results, whether patentable or not, shall be in accordance with the terms and conditions set forth in the Clinical Study Agreement by and between the Institution and Sponsor. Unless otherwise expressly set forth in the Clinical Study Agreement, the Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries and any other information collected during this study. The Sponsor reserves the right to use the data from the database in the present study.

15.7. Direct Access to Source Data/Documents

By participating in this registry, the Investigator/site agrees to permit study-related monitoring, audits, IEC review, and regulatory inspection, and provide Sponsor, Sponsor representative, auditors, and regulatory authorities access to source data/documents, as applicable. If an Investigator is notified of a pending investigation by a regulatory agency, standards organization, or other similar organization, he/she will inform the Sponsor promptly.

All subject treatment, follow-up visits and phone interviews will be properly documented and considered to be source. Source documentation may be found in the subject's medical records or in the subject binder. Additional subject medical record review may be required. De-identified source documents and medical records may be photocopied, if required.

15.8. Confidentiality

The Investigator shall consider all information, results, discoveries; records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential

and shall not disclose any such results, discoveries, records to any third party without the Sponsor's prior written consent.

The Investigator will make all required efforts to ensure that patient information remains confidential. The primary means by which this is accomplished is by 1) not using any identifying information in registry records other than subject ID number, and 2) removing identifiers from all medical record information (i.e., source documentation) submitted for the registry.

IEC members have the same obligation of confidentiality.

15.9. Liability

The Sponsor will maintain appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the IEC.

15.10. CIP Amendments

During the course of the registry, an amendment to the CIP may be necessary. Only the Sponsor is allowed to amend the CIP. Any amendments or modifications must be approved by the IEC prior to implementation. The investigation sites will receive the following for their regulatory file, and if applicable, IEC submission:

- A memorandum outlining the changes and justification for modifications
- An updated protocol
- Updated appendices (if necessary)
- Updated ICF template (if necessary)

15.11. Record Retention

15.11.1. Investigator Record Retention

All study-related documents must be retained for a period required per local regulation. Medtronic will inform the primary investigator/site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The primary investigator should take measures to prevent accidental or premature destruction of documents. If the PI is no longer participating in the registry, the responsibility of conducting follow-up and maintaining records (including applicable source documents, CRFs, investigator site file, electronic data etc.) must be transferred to another responsible party within the

institution (i.e., Sub-I). Notice of transfer must be provided in writing by the PI to the Sponsor and the IEC no later than 10 working days prior to the transfer.

15.11.2. Sponsor Record Retention

The Sponsor will maintain all study documentation in its possession and/or contact and institute measures to prevent accidental or premature destruction of any data and/or documents related to the research study.

The Sponsor shall retain the study documentation in accordance with Medtronic Record Retention Policy, GCP requirements and local regulations in force in the Sponsor's jurisdiction, after formal discontinuation of study.

15.12. Publication and Use of Information

The Sponsor intends to publish the results of this multi-center study. Individual Investigators are therefore asked to refrain from reporting results from their study participants prior to publication of the main multi-center report. The development of publications from the PROSPR-SEA Registry is detailed in the PROSPR-SEA Registry Publication Plan and will indicate the conditions under which, the results of the study will be submitted for publication. The purpose of the publication plan is to facilitate the production of timely, high quality publications, avoid inconsistencies and redundancies in publications, protect the scientific integrity of the data, and provide authorship guidelines such that all Investigators have the opportunity to participate in and receive appropriate publication credit for the presentation of data from the PROSPR-SEA Registry. The publication plan includes committee composition, primary and secondary publications topics, authorship policy, target conferences/journals, etc.

The Sponsor will register and submit the results for the registry on *clinicaltrials.gov*.

15.13. Suspension or Early Termination

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all PIs of the termination or suspension and the reason(s) for this. The PI shall then promptly inform the reviewing IEC and provide the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled subjects will be asked to complete all remaining study visits and the subject will then be seen by the treating physician according to standard care following endovascular treatment.

The Sponsor, IEC or regulatory authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing IEC, non-compliance to the CIP or lack of enrollment). If an investigation site is suspended or prematurely terminated, the Sponsor shall promptly

inform the Investigator(s) of the termination or suspension and the reason(s). The Investigator shall then promptly inform the reviewing IEC.

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17. Appendices

N/A

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• 'Not Applicable, New Document'	[redacted] Associate Clinical Research Manager