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CLINICAL INVESTIGATIONAL PLAN

Feasibility Study of the treatment of Acute Ischemic Stroke using the NOVIS Transcarotid Neuroprotection System In Transcarotid Embolectomy.

The NITE 1 Study

Clinical Protocol	SRM–2019-01
Version	E
Version Date	May 15, 2023

NCT Number: 04881162

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PROTOCOL SIGNATURE PAGE

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I have read this protocol and agree to adhere to the requirements. The protocol, other study documents and all necessary information will be made available to trained study staff (Investigators, Neurologists, Coordinators, etc.). As required, will discuss this material with them and ensure they are fully informed regarding the study device and protocol. The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), ISO 14155, Declaration of Helsinki, and all applicable regulatory requirements, and to the Institutional Review Board (IRB) requirements.

Study Site Name	Site Location (City, State)
Principal Investigator Printed Name	
Principal Investigator Signature	Date

Table of Contents

1 Protocol Summary

Title	Feasibility Study of the treatment of Acute Ischemic Stroke using the NOVIS Transcarotid Neuroprotection System In Transcarotid Embolectomy. (The NITE 1 Study)
Study Objective	To establish the feasibility and safety of the NOVIS Transcarotid Neuroprotection System when used for the transcarotid intervention of patients that have a failed transfemoral endovascular therapy in the case of anterior circulation strokes due to large vessel embolic occlusions.
Study Design	A prospective, multi-center, single arm feasibility study for the endovascular treatment of patients with acute ischemic anterior circulation strokes due to large vessel embolic occlusions using the transcarotid approach with flow reversal. Patients enrolled into the NITE 1 Study will have failed transfemoral therapy and will be followed immediately from post-op to 90 days.
Enrollment	A minimum of 30 and a maximum of 40 study patients will be enrolled into the per protocol population (reference Section 14.1 for definition).
Investigation Site Locations	Up to 8 sites in the United States of America.
Primary Outcomes	• Device-related Serious Adverse Events – vascular complications including dissection, pseudoaneurysm, hematoma, arteriovenous fistula, thrombus formation, embolization and any vascular complication that may be attributed to the device AND requires surgical repair, surgical wound revision, transfusion, etc. • Other Serious Adverse Events – permanent cranial nerve injury, new symptomatic ipsilateral hemorrhage and dissections related to ancillary devices. • Functional independence measured at 90-day mRS (proportion with mRS score 0-2)
Secondary Outcomes	• Carotid access time • Time to final revascularization • Device-related complications • Neurologic assessment at 90 days (proportion of patients with a nondisabling or disabling stroke according to NIHSS) • Technical success rates • Rates of revascularization success (mTICI ≥ 2b)
Patient Population	Patients with acute ischemic anterior circulation stroke due to large vessel embolic occlusion who are candidates for endovascular therapy and in whom transfemoral therapy failed.
Planned Schedule	Commence Enrollment: Q3 2021 Complete Enrollment: Q3 2022 *(estimated)* Complete 90-day Follow-Up: 90 days following last enrollment Issue FDA Final Report: Q4 2022 *(estimated)*

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3 Introduction

3.1 Background

Nearly 800,000 strokes occur in the United States each year. Of these, approximately 87% are considered ischemic strokes (Benjamin et al. 2019). About three-quarters of all strokes occur in persons aged ≥65 years. Age remains the most non-modifiable risk factor for stroke, and the risk continues to double every 10 years after the age of 55 (Yousufuddin et al. 2019). Although stroke mortality during the past 10 years has declined, it is still the fifth leading cause of death. Stroke is the leading cause of permanent disability and one of the most frequent causes of vascular dementia in the developed world (Benjamin et al. 2019). Large vessel occlusions (LVOs) are ischemic strokes that result from a blockage in one of the major proximal arteries of the brain. These large vessels include the basilar artery, carotid terminus and middle cerebral artery, and occlusions therein cause loss of blood flow to significant portions of the brain.

Since the 1990s, the only proven treatment of acute ischemic stroke (AIS) was intravenous thrombolysis (IVT) with tissue-type plasminogen activator (tPA). However, its use is limited by several factors like the narrow time window after stroke onset during which it has been found to be safe and effective from randomized trials and the fact that its use is associated with only a moderate recanalization rate, especially in the larger proximal cerebral arteries (Papanagiotou MD et al. 2018). Major breakthroughs in endovascular treatment of acute stroke occurred in 2015,

when endovascular therapy/thrombectomy became the standard of care after 5 prospective randomized trials demonstrated consistent benefit in selected patients with AIS (Hasan et al. 2018). These trials concluded convincingly that endovascular thrombectomy dramatically improves the 90-day functional outcomes of eligible patients. MR CLEAN was the first randomized control trial to report beneficial results for endovascular therapy (EVT) in acute ischemic stroke. This study was followed by additional positive trials EXTEND-IA, ESCAPE, SWIFT PRIME, and REVASCAT with consistent outcome benefit for EVT. These trials established EVT for patients presenting 0-8 hours after symptom onset (Papanagiotou MD et al. 2018).

The most recent paradigm shift in AIS care for patients with LVOs was seen in 2018 with the completion of the DAWN and DEFUSE 3 trials. These studies established EVT for patients with emergent large vessel occlusions presenting 6 to 24 hours after symptom onset. As a result, current American Heart Association guidelines recommend EVT for patients with AIS within 6-16 hours and is considered reasonable for 16-24 hours (Powers et al. 2019). This shift was attributable partly to the efficacy of stentrievers in clot extraction, but largely to the appropriate selection of patients with salvageable brain tissue, based on multimodal imaging and limiting inclusion to strokes with small infarct cores(Dolia et al. 2019).

In a 2018 meta-analysis of patient-level data from MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE , the HERMES collaboration reported that endovascular therapy achieves better outcomes at 90 days than standard medical therapy across a broad range of imaging categories including ASPECTS <6 (San Román et al. 2018).

Direct suction aspiration of the thrombus also has been developed as an alternative technique to the use of stentrievers. Randomized trials such as ASTER and COMPASS have shown no difference between suction aspiration and stentrievers as a first-line strategy on any angiographic, clinical or safety outcome(Zhu et al. 2018). New aspiration systems have continually developed, resulting in larger inner diameters of the aspiration catheters. The aspiration technique is used in some centers as a primary approach for treating intracranial large vessel occlusions (Papanagiotou MD et al. 2018). Recently developed techniques simultaneously use the stentrievers and the aspiration catheter at once to enhance the efficacy of recanalization. Combined therapies, commonly referred to as the SOLUMBRA technique, are being evaluated in trials such as ASTER 2 (Zhu et al. 2018).

EVT for acute ischemic stroke is most commonly performed through transfemoral access. The preference for this approach is related to the compressibility of the common femoral artery, to the fact that via this approach all great vessels from the aortic arch can be catheterized and in addition, selective catheterization of the great vessel branches (internal carotid arteries for example etc.) can be performed and thus multiple potential sites of occlusion can be accessed (Jadhav et al. 2014). It should be appreciated that almost all endovascular devices were originally formulated to be inserted via a transfemoral access point in the era of coronary catheterization and angioplasty (percutaneous coronary intervention; PCI). Barriers to great vessel/carotid/vertebral/intracranial vessel access and inadequate guide catheter support can impede or prevent device delivery to the face of the thrombus. Significant peripheral vascular disease can make traditional femoral artery access either time consuming or impossible, necessitating alternative approaches or causing early termination of the thrombectomy procedure, risking a poor clinical outcome. Similarly, in patients with certain aortic arch configurations (e.g., type III or “bovine”) or with significant cervical vascular tortuosity, catheterization may be significantly delayed, and placement of large-bore guide catheters may be

impossible (Yoo et al. 2017). The presence of significant arch atheroma burden (which increases with age) renders transfemoral access risky in terms of embolization from the arch during catheter/guidewire manipulations.

Ribo et al. performed an analysis of 130 patients undergoing endovascular procedures for acute stroke which showed that 5.4% of the patients could not be successfully catheterized via transfemoral access. A negative correlation was found between time to carotid access and final recanalization; patients with difficult access had a lower rate of recanalization. Moreover, patients with difficult catheter access also had a significantly longer procedure time but similar time from symptom onset to final recanalization meaning that catheterization of the arch and great vessel origins from a transfemoral approach is the rate limiting step. Based on this study, patients with difficult catheter access had longer procedures, lower recanalization rates and poorer outcomes at 90 days(Ribo et al. 2012).

In AIS from LVO, timely recanalization of proximal intracerebral vessels can minimize long term disability by salvaging the at-risk ischemic penumbra around the infarct core and, consequently, reducing the associated morbidity and mortality (Papanagiotou MD et al. 2018). Several studies have emphasized that procedure time in stroke patients undergoing endovascular intervention (vascular access to recanalization) is a critical determinant of long-term outcomes. Difficult catheter access, which may contribute to delays in revascularization, has been associated with lower recanalization rates and poor clinical outcomes. Prolonged groin to reperfusion time due to technical difficulties in catheterizing proximal supraaortic vessels leading to termination of EVT are also associated with higher severity of poststroke disability and reduced rate of functional independence (Jadhav et al. 2014).

Every hour of delay has been shown to result in an absolute 6.4% decrease in the probability of a good outcome by EVT, measured as the risk difference between intervention and control (Ribo et al. 2012). Ribo et al. showed that failure of transfemoral catheterization occurred in up to 5% of patients and that this was associated with a delay of more than 30 minutes until vessel recanalization, thereby worsening clinical outcomes.

Patients with difficult catheter access also had a significantly longer procedure time (groin puncture to recanalization) but similar time from symptom onset to final recanalization. Ribo et al. created a risk factor-based scoring system to calculate the chances of difficult femoral access in advance of the procedure. The scoring system focuses on four variables that individually and in combination are significantly associated with difficult access, primarily due to elongated and tortuous vessel anatomy: age >75 years, hypertension, dyslipidemia and left carotid access. A point is added for every risk criterion that the subject is associated with and a score of >2 was found to be predictive of difficult catheter access with 84% sensitivity and 74% specificity (Ribo et al. 2012).

In order to avoid the limitations posed by the transfemoral access, alternative access routes including transradial, transbrachial, transcervical vertebral and transcarotid approaches have been reported in order to treat acute ischemic stroke. While some have performed a percutaneous puncture of the common carotid artery, others have reported a direct (open) carotid approach preceded by surgical cutdown (Styczen et al. 2019). Published experiences of endovascular treatment of acute stroke via the transcarotid approach have shown that surgical carotid access for endovascular stroke treatment is feasible, with considerable advantages, in patients with expected problematic access or for whom transfemoral endovascular carotid access has failed (Wiesmann et al. 2016). As such, the current American Stroke Association (Powers et

al. 2019) guidelines recommend that alternate routes, including transradial, transbrachial, and direct carotid puncture, are technically feasible and should be employed as necessary to obtain recanalization (Gandhi et al. 2018). However, there is an increased risk of arterial injury and postoperative arterial occlusion due to the smaller diameter of the brachial and radial arteries (Wiesmann et al. 2016).

3.2 Summary of Relevant Publications and Clinical Studies for the Transcarotid Approach for AIS

In 2014, Jadhav et al. reported a series of seven cases in which access was achieved via percutaneous puncture of the carotid after initial attempts via the transfemoral artery were unsuccessful. A skin incision was necessary to both facilitate catheter advancement and permit the redundant cervical epidermis from being pulled into the arteriotomy. All patients achieved recanalization with 87.5% of patients achieving ≥50% reperfusion (Jadhav et al. 2014).

Mokin et al. reported two cases in which a direct, percutaneous carotid approach was used for endovascular stroke treatment with favorable results. In one of these two patients, reperfusion with good clinical outcome was achieved in 25 minutes (Mokin et al. 2015).

In 2016, Wiesmann reported a retrospective analysis of six cases that used surgical access to the carotid artery and consecutive transcarotid endovascular thrombectomy in patients with acute ischemic stroke with all patients achieving intracranial recanalization. There was one small hematoma reported due to post-operative oozing, but no other access-related or endovascular therapy related events were reported (Wiesmann et al. 2016).

Larrazabal performed a carotid cutdown and direct, controlled puncture of the carotid artery for the treatment of intracranial aneurysms and carotid artery stenosis in four patients. The carotid artery access was also repaired surgically under direct visualization. There were no access site related complications nor cardiac, systemic, or neurologic events. The authors concluded that transcarotid access with surgical exposure of the carotid artery for direct and controlled vascular puncture is an effective alternative for endovascular extracranial and intracranial procedures in patients in whom the femoral route cannot be used (Larrazabal et al. 2010).

Cord et al. reported a retrospective analysis of 352 mechanical thrombectomy (MT) procedures attempted mostly via transfemoral approach between 2015 and 2018, of which 37 cases were deemed to have prohibitive vascular access and divided into two groups. One subset included aborted MT attempts (n=17) that failed transfemoral access due to the inability to reach the clot. The second subset included direct carotid puncture cases (n=20) that were attempted either as a salvage technique following a failed transfemoral MT attempt or failed transfemoral MT due to operator discretion following review of the preintervention CTA. In the direct carotid puncture subset, successful reperfusion was achieved in 84% of cases, and complications included inability to catheterize the carotid artery in one patient, neck hematomas in four patients, non–flow-limiting common carotid artery (CCA) dissections in two patients, and a delayed, fatal carotid blowout in one patient. When comparing the two subsets, patients in the direct carotid puncture group had smaller infarct volumes (11 vs. 48 mL, p = 0.04), a greater reduction in NIHSS score (−4 vs. +2.9, p = 0.03), and better functional outcome (shift analysis for 3-month modified Rankin Scale score: adjusted OR 5.2, 95% CI 1.02–24.5; p = 0.048), advocating for the use of direct carotid puncture among emergency MT patients with anterior circulation AIS-LVO and prohibitive vascular access (Cord et al. 2020).

While recanalization can be achieved using the percutaneous carotid approach, closure of the carotid puncture site remains an unsolved problem, as none of the available closure devices used for transfemoral closure have been approved for carotid closure. Local puncture-related complications (dissections and local hematomas) after percutaneous carotid puncture have been reported in 2.4–10.7% of cases in a large series (Wiesmann et al. 2016). Mokin also reported that percutaneous puncture of the carotid artery without direct visualization could result in perpendicular placement of the sheath into the carotid artery causing kinking of the sheath, which made subsequent aspiration catheter delivery and aspiration thrombectomy less efficient (Mokin et al. 2015). This may suggest that surgical cutdown of the carotid artery may facilitate placement of the sheath. Carotid access enabled by direct neck exposure also allows for the use of a large-caliber catheter and the access site can be safely closed under direct visualization while checking for bleeding, dissection and subsequent hematomas (Lee et al. 2018).

Given the overall smaller risk of local complications of surgical cutdowns compared with percutaneous puncture, various authors strongly recommended surgical cutdown instead of percutaneous puncture of the carotid artery in order to reduce the risk of vessel injuries, in particular when patients have vascular fragility (Wiesmann et al. 2016).

Regarding alternative vascular access, regardless of a percutaneous or surgical approach, the inability to safely place the guiding catheter, which is the main cause of technical failure in transfemoral neurointerventions, is overcome with a direct carotid approach. The direct carotid approach also offers a short access route, which represents both a mechanical and temporal advantage because it renders the endovascular navigation quicker and easier (Larrazabal et al. 2010).

3.2.1 Transcarotid Artery Revascularization (TCAR)

Since its introduction in the 1950s, carotid endarterectomy (CEA) has been the gold standard for stroke prevention in patients presenting with neurological deficits secondary to embolization from the internal carotid artery and in patients incidentally found to have high grade asymptomatic extracranial internal carotid artery stenoses. Transfemoral carotid stenting was introduced as a less invasive alternative to carotid endarterectomy in 1996 to decrease perioperative morbidity and mortality. While this alternative has been associated with a lower perioperative risk of myocardial infarction and cranial nerve injury compared to CEA, several randomized controlled trials have found significantly higher risk of perioperative stroke/death.

TCAR was developed to address several areas of concern with transfemoral carotid stenting: first, iatrogenic embolization from manipulation of the aortic arch when attempting to cannulate the carotid artery; second, use of long sheaths and catheters to reach the carotid lesion; third, embolization during unprotected crossing of the carotid lesion to deploy a distal embolic filter-type protection device; and finally, embolization around an incompletely apposed filter or through the micropores of the filter (filter peri-flow and through-flow).

In 2009, Silk Road Medical, Inc., initiated a first-in-human trial to evaluate the safety and performance of a dedicated system that facilitates carotid revascularization via the transcarotid approach using flow reversal as the embolic protection mechanism. The device was later evaluated in 2 separate clinical studies as described below.

Briefly described, for the ENROUTE NPS TCAR procedure, an arterial sheath is placed under direct surgical visualization into the common carotid artery proximal to the carotid bifurcation and a venous return sheath is placed percutaneously in the femoral vein. The two sheaths are connected by a flow controller line and filter creating an arteriovenous shunt. Once the systems are in place, the common carotid artery is clamped just proximal to the arterial sheath insertion site. Once antegrade flow is obstructed, the differential in the arterial and venous pressures causes the blood flow to reverse from the brain, entraining oxygenated blood across the Circle of Willis from unclamped territories, out through the external flow line with the blood returned to the femoral vein after passing through an external 200 micron filter. With the protection of flow reversal initiated, the EVT can be performed while emboli are directed away from the brain. The NOVIS NPS NITE (Neuroprotection in Transcarotid Embolectomy) procedure is slightly modified from the ENROUTE NPS TCAR procedure, since EVT is focused on the removal of an anterior circulation LVO vs. balloon angioplasty and stenting a carotid bifurcation. However, both procedures establish flow reversal as a protection mechanism before initiating EVT.

3.2.2 ROADSTER Study

In 2012, Silk Road Medical initiated the ROADSTER study, a multicenter trial of 219 patients to evaluate the safety and effectiveness of the ENROUTE Transcarotid Neuroprotection System (ENROUTE NPS) with all FDA-approved carotid artery stent systems. The ROADSTER study showed a low overall 30-day stroke/death rate of 2.8% and a 30-day stroke rate of 1.4%. It was the lowest reported stroke rate of any multicenter trial of carotid revascularization with independent adjudication. The ROADSTER study supported 510(k) clearance of the ENROUTE NPS in 2015.

The rate of serious arterial dissections (those requiring treatment) in the ROADSTER study was 1.8% (4/219). The rates of arterial dissection deemed to be serious in nature vary across contemporaneous studies of carotid artery stenting and embolic protection devices as shown in Table 1.

Table 1. Rates of Serious Dissection and Hematomas

	ROADSTER	Abbott Acculink (ARCHeR) P040012[1]	Abbott Xact (SECuRITY) P040038	Boston Scientific Wallstent (BEACH) P050019	Covidien Protégé (CREATE) P060001	Cordis Precise (SAPPHIRE) P030047
Serious Dissection Rate	1.8%	0.0%, 0.72%, 2.07%	3.28%	0.4%	1.2%	Not Reported
Serious Wound/Groin Hematoma	2.3%	Not Reported	Not Reported	2.1%	Not Reported	Not Reported

As these results show, the rate of serious dissection in the ROADSTER study is within the range reported in other pivotal carotid artery stenting and embolic protection device trials (0.0%-3.28%). The rate of serious wound hematoma (defined as non-arterial surgical wound hematomas requiring treatment) was 2.3% (5/219) in the combined population (pivotal and extended enrollment). There were no serious groin hematomas (defined as femoral vein access site hematomas) in the ROADSTER study. Wound/groin hematoma rates are rarely reported in other contemporaneous CAS and EPD studies and thus reports of this event are under-reported in TF-

[1] Rates include ARCHeR 1, 2 and 3 respectively

CAS studies. As a result, direct comparisons against TCAR may not be valid. The BEACH study (Boston Scientific Carotid Wallstent) reported a discreet hematoma rate of 2.1%, and the ROADSTER serious wound hematoma rate is comparable to this rate. The variable definitions and reporting standards for local complications make direct comparisons complex.

While wound/groin/access site hematomas are rarely reported separately, most contemporaneous carotid artery stenting and embolic protection device studies do report on serious access site complications or serious vascular complications, which represent varying composites of bruising, hematoma, bleeding and vascular injury. However, there is no apparent harmonization of the definitions and it is difficult to discern how each of the individual elements of the composite contribute to the overall rates of occurrence. That said, the following table presents the rates of serious access site complications from contemporaneous carotid artery stenting and embolic protection device studies that are incremental to the wound hematoma and dissection rates tabulated above, unless they were otherwise not reported. Data for the pivotal stent trials are reported in the respective Summaries of Safety and Efficacy Data on the FDA website.

Table 2. Rates of Serious Access Site Complications

	ROADSTER	Abbott Acculink (ARCHeR) P040012[2]	Abbott Xact (SECuRITY) P040038	Boston Scientific Wallstent (BEACH) P050019	Covidien Protégé (CREATE) P060001	Cordis Precise (SAPPHIRE) P030047[3]
Serious Access Site Complications	2.3%	5.70%, 4.68%, 2.76%	2.62%	NR	2.6%	5.4%, 2.5%

For the ROADSTER study, access site complications were a secondary endpoint as reported above with a tabulation that is redundant to separately reported adverse events and serious adverse events. The five (5) events reported in this tabulation of serious access site complications (Table 2) are the same events reported in the serious wound hematoma tabulation and discussion above.

There were no serious or non-serious pseudoaneurysms reported in the ROADSTER study. In comparison, the rate of pseudoaneurysm has been reported to be 0.4% in the BEACH study (Boston Scientific Carotid Wallstent). Data from the ROADSTER study show that direct carotid access for extracranial carotid revascularization in patients with significant anticoagulation (to an ACT of ≥ 250 seconds) and dual antiplatelet medications is safe and effective.

The secondary endpoints demonstrate that the device has a high rate of acute, technical and procedural success (99.3%, 99.3%, and 95.7% respectively) and low rate of serious access site complications (0.7%). Furthermore, the non-hierarchical rates of events for all death (1.4%) and all stroke (1.4%) are equivalent to the hierarchical event rates for death and stroke respectively, meaning that there were no stroke related deaths. There were no major or hemorrhagic strokes in the ITT population. There was one cardiac death (0.7%) and one death due to sequelae from respiratory failure (0.7%).

[2] Rates include ARCHeR 1, 2 and 3 respectively
[3] Rates include randomized and non-randomized arms respectively

3.2.3 ROADSTER 2 Study

In October 2015, Silk Road Medical initiated the ROADSTER 2 Post-Approval Study, a multicenter study of 692 patients. Results of this study were submitted to FDA on November 25, 2019 via P140026/R013. The primary endpoint was the rate of procedural success at 30 days following the index procedure. Procedural success is defined as acute device success (successful insertion of the ENROUTE NPS and establishment of flow reversal), technical success (deployment of interventional tools) and the absence of a major adverse events (hierarchical stroke/death/myocardial infarction) through 30 days. This study demonstrated a high procedural success rate of 97.9%. High rates of acute device and technical success were demonstrated at 99.7% for both.

The hierarchical major adverse event rate (stroke/death/myocardial infarction) in ROADSTER 2 was 1.7%. The incidence of combined stroke/death was 0.8%. There was one (1) death (0.2%) which was unrelated to both the study device and procedure. That patient expired from a ruptured abdominal aortic aneurysm approximately two weeks following treatment in ROADSTER 2.

There were ten (10) acute cranial nerve injuries reported in the ITT population of ROADSTER 2 (1.4%). Six (6) of ten (10) patients returned for extended follow-up and all cranial nerve injuries had resolved. The resolution of cranial nerve injuries for four (4) patients is unknown, since these patients did not consent to additional follow-up.

There were eight (8) adverse events that were attributed to the study devices (1.3%) including seven (7) arterial dissections (1.1%) and one (1) thrombosed stent (0.2%). The arterial dissection rate in ROADSTER 2 was lower than that of ROADSTER, as ROADSTER 2 used a second-generation device designed to be more atraumatic. In a recent publication comparing TCAR to transfemoral CAS, TCAR was associated with a lower rate of technical failure compared to transfemoral CAS (0.5% vs 1.2%; p<.001)(Schermerhorn et al. 2019).

There were no reports of unanticipated adverse device effects in ROADSTER 2.

TCAR with reverse flow has proven to be a safe and effective treatment for carotid revascularization. With over 20,000 procedures performed worldwide, physician utilization of TCAR has started to evolve into other therapeutic areas for the benefits of the access and the protective aspects of reverse flow.

3.2.4 Procedural Times

The average time from skin incision to cannulation of the common carotid artery (CCA) was 13 minutes in the ROADSTER study population (excluding aborted cases). In ROADSTER 2, mean procedure time was 74.8 minutes (skin incision to skin closure). This is comparable to the mean procedure time for transfemoral CAS of 69 minutes as reported in the CREST study(Vilain et al. 2012). Procedure time was not defined in the CREST study.

3.2.5 Anticoagulation

Several studies have been conducted to evaluate the safety of intraprocedural anticoagulation in the acute ischemic stroke (AIS) patient population. A few representative studies are summarized below, which largely demonstrate no difference in functional outcomes and rates of symptomatic

intracranial hemorrhage (sICH) among patients who receive intraprocedural anticoagulation and those who do not.

The TREVO 2 trial (Winningham et al. 2018) evaluated 173 AIS patients who underwent clot retrieval using the Merci coil retriever and Trevo stent retriever. The mRS at 90-days was independently associated with patients who received a heparin bolus, and the rate of TICI 2b/3 reperfusion and intracranial hemorrhages were similar between those who received and did not receive intraprocedural heparin. Another study (Farook et al. 2016) stratified the use of intra-procedural heparin among 76 AIS patients with MCA M1- or ICA-T occlusion and found significantly lower rates of hemorrhage among the heparin group (p=0.02). Finally the MR CLEAN registry, a multi-center prospective registry(Van De Graaf et al. 2019), presented data on 1,488 patients with ICA, ICA-T, MCA-M1, MCA-M2, ACA-A1 or ACA-M2 occlusions demonstrating no significant difference among patients treated with intravenous heparin and those without in functional outcomes (adjusted common odds ratio, 1.17; 95% CI, 0.87–1.56), successful recanalization (adjusted odds ratio, 1.24; 95% CI, 0.89–1.71), sICH (adjusted odds ratio, 1.13; 95% CI, 0.65–1.99), or mortality (adjusted odds ratio, 0.95; 95% CI, 0.66–1.38). However, site level analysis showed sites that used heparin more often, also had better functional outcomes (adjusted common odds ratio, 1.07 per 10% more heparin, 95% CI, 1.01–1.13). On the other hand, a Chinese study (Yang et al. 2019), presented an analysis on 619/917 patients from the ANGEL registry, which showed an increased risk for sICH and embolization and lower functional independence with heparinization (9.3 vs. 5.1%, adjusted p = 0.02; 7.1 vs. 3.1%, adjusted p = 0.04, respectively), although recanalization rates, total ICH, and long-term mortality did not differ between the heparinized and non-heparinized groups (adjusted p > 0.05 for all). In conclusion, the summary of these multiple data sets demonstrates comparable outcomes among patients who do and do not receive intraprocedural anticoagulation across functional outcome, sICH, and mortality.

As a result, the sponsor does not believe patients are at any additional risk based on who has or has not received anti-coagulants during the procedure. With the exception of the required use of the pressurized, heparinized saline bag in section 10.3.3, the use of procedural anticoagulation has been carefully considered and will be left to the discretion of the operator.

4 Investigational Study Plan

4.1 Objectives

The objective of this study is to demonstrate the feasibility and safety of the NOVIS Transcarotid NPS when used for the transcarotid intervention of patients that have failed transfemoral endovascular therapy in the case of anterior circulation strokes due to large vessel embolic occlusions.

5 Device Overview

5.1 Device Description

The NOVIS Transcarotid Neuroprotection System (NPS)

The NOVIS Transcarotid Neuroprotection System is a modified version of the ENROUTE NPS. The NOVIS Transcarotid NPS consists of four primary components:

- Transcarotid Arterial Sheath with Arterial Dilator
- Venous Return Sheath with Venous Dilator
- Flow Controller with Filter
- 0.035” Extra Support, J-Tip Guidewire

When assembled, the NOVIS Transcarotid NPS creates an arteriovenous shunt that can reverse the flow of blood in the carotid artery from antegrade to retrograde, shunting embolic particles away from the cerebral circulation during endovascular interventions (see Figure 1 below). The NOVIS NPS is intended to provide vascular access and embolic protection during treatment with neurothrombectomy devices; it is not intended to aspirate the carotid artery and its branches or to perform mechanical neurothrombectomy at a distance from the site of occlusion.

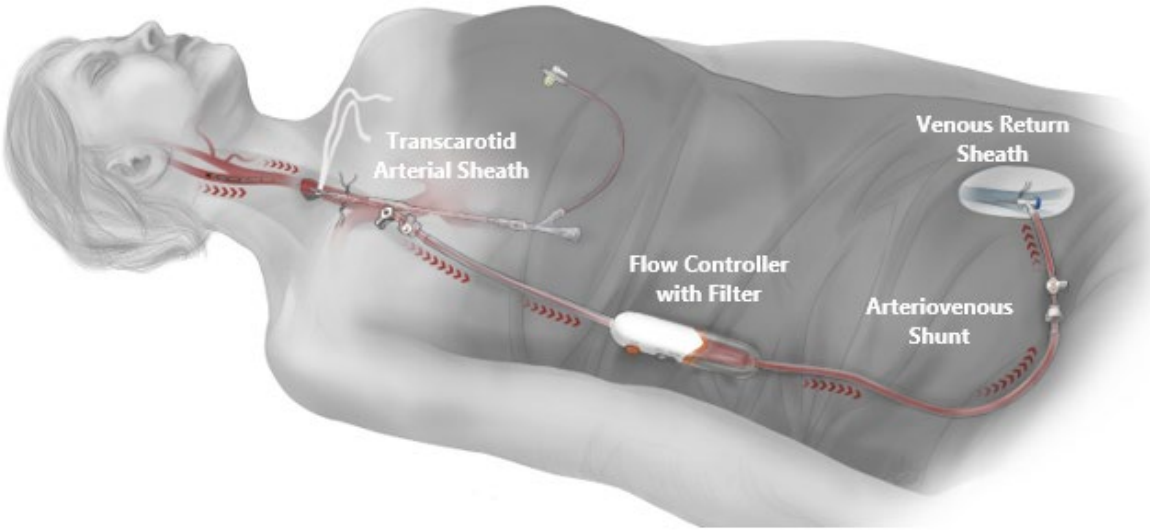


Figure 1. NOVIS Transcarotid Neuroprotection System

Key dimensions of the NOVIS Transcarotid NPS are listed in Table 3 and include lengths and diameters of each component.

Table 3. Key Dimensions of the NOVIS Transcarotid Neuroprotection System

Attribute	Transcarotid Arterial Sheath	Venous Return Sheath	Arteriovenous Shunt**
Working Length	11 cm (4.3 in)	11 cm (4.3 in)	
Total Length	33.2 cm (13.1 in)	13.6 cm (5.4 in)	102 cm (40.2 in)
Inner Diameter	Sheath Tip ID: 8 Fr (2.7 mm/0.105 in)	Sheath Tip ID: 8 Fr (2.7 mm/0.105 in)	
Outer Diameter	10.5 Fr	10.5 Fr	

Attribute	Transcarotid Arterial Sheath	Venous Return Sheath	Arteriovenous Shunt**
	(3.5 mm/ 0.136 in)	(3.5 mm/ 0.136 in)	

** The Arteriovenous Shunt total length includes the large diameter tubing from the Arterial Sheath to the Venous Return Sheath.

Each component of the NOVIS Transcarotid NPS is described in the following sections.

5.2 Transcarotid Arterial Sheath

The NOVIS Transcarotid Arterial Sheath with Uber-Flex™ Tip consists of an 8 Fr. Arterial Sheath and an Arterial Dilator (see Figure 2). The Transcarotid Arterial Sheath permits access to the common carotid artery (CCA), and includes the following features:

- A radiopaque tip which allows visualization of the sheath tip under fluoroscopy.
- Printed centimeter markers to measure sheath insertion depth.
- An extension tube which extends the proximal end of the Arterial Sheath away from the radiation field.
- A female luer connection on the proximal end of the extension tube for the attachment of a Rotating Hemostasis Valve (RHV). The RHV (not included) will provide hemostasis after Dilator removal, allow introduction of interventional devices into the Arterial Sheath and enable continuous heparinized saline flush.
- Suture Eyelets for securement of the Arterial Sheath.
- An Arterial Stopcock which connects the Arterial Sheath to the Flow Controller via a “quick connect” type fitting. The handle on the Arterial Stopcock is used to shunt flow once the Arterial Sheath is connected to the Flow Controller.

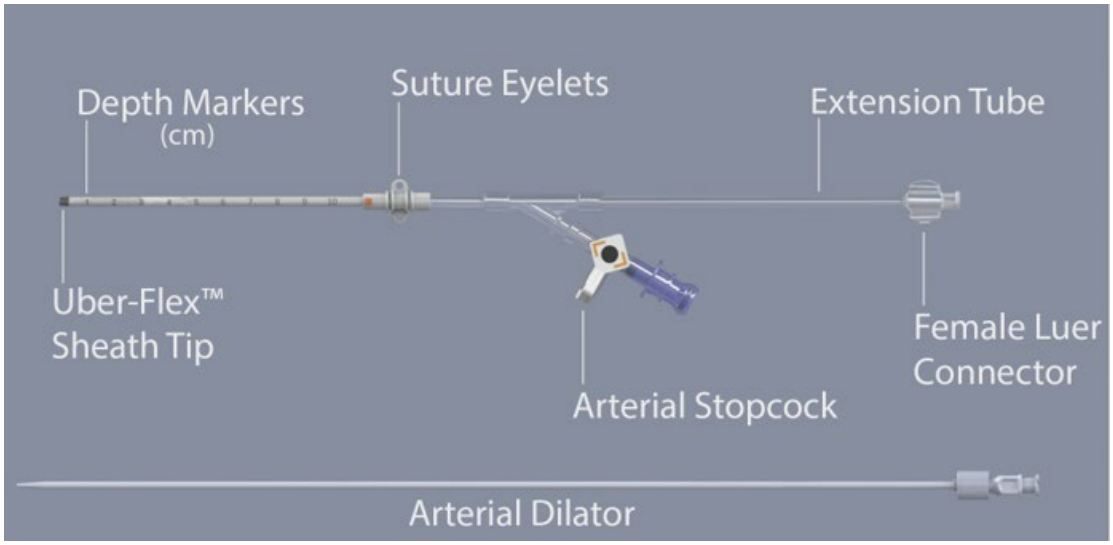


Figure 2. NOVIS Transcarotid Arterial Sheath and Dilator

5.3 Venous Return Sheath

The NOVIS Venous Return Sheath consists of an 8 Fr. Venous Sheath and a Venous Dilator (see Figure 3). The Venous Return Sheath is used to gain femoral vein access, and includes the following features:

- A radiopaque tip which allows visualization of the sheath tip under fluoroscopy.
- A Hemostasis Valve on the proximal end of the Sheath to provide hemostasis after removal of the Dilator.
- Suture Eyelets for securement of the Venous Return Sheath.
- A Venous Flow Line and Stopcock which connects the Venous Return Sheath to the Flow Controller via a “quick connect” type fitting. The Venous Stopcock also permits saline prep, saline and contrast injections, and aspiration.

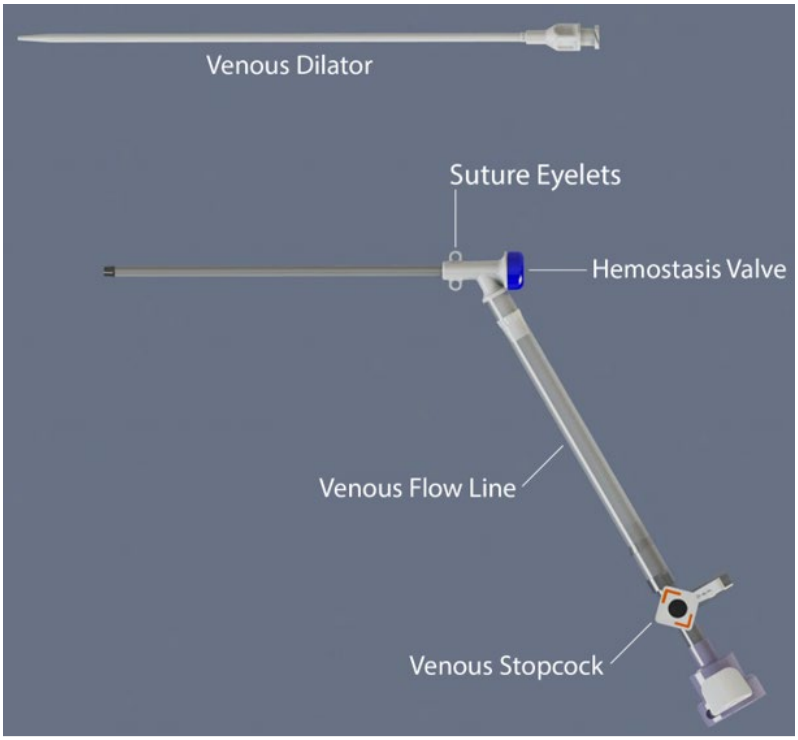


Figure 3. NOVIS Venous Return Sheath

5.3.1 Flow Controller

The NOVIS Flow Controller (see Figure 4) connects the Transcarotid Arterial Sheath to the Venous Return Sheath and includes the following features:

- A Flow Controller which regulates the rate of reverse flow via the High/Low Switch and which allows temporary shut off of the Controller/Filter Line during contrast injections via the Flow “Stop” Button (detail in Figure 5). Pressing the switch towards “Low” sets the flow setting to low flow and pressing the switch towards “High” sets the flow setting to high flow.
- An in-line Filter which captures embolic debris from the blood flow through the shunt.
- An in-line Check Valve which prevents inadvertent flow or injection of blood or fluid through the shunt in the arterial direction.
- “Quick-Connect” type connections to the Transcarotid Arterial Sheath and Venous Return Sheath.
- A “Pull to Prep” Toggle Loop that is removed and discarded prior to system prep and usage.

Figure 4. NOVIS Flow Controller

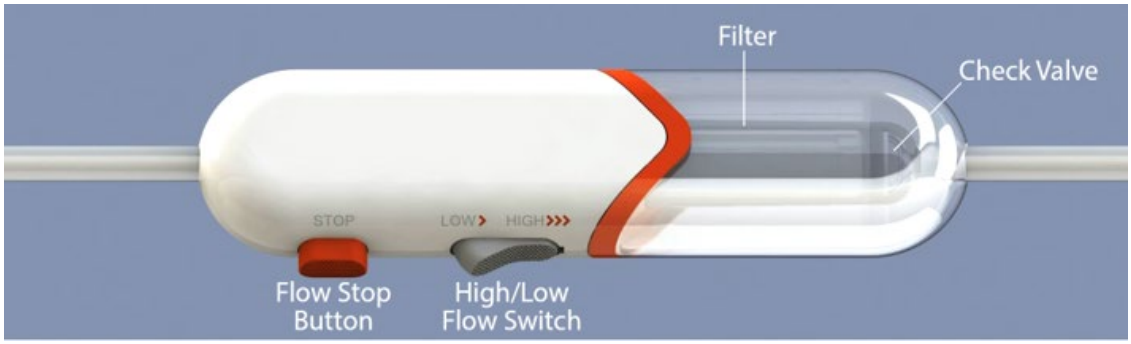


Figure 5. Flow Controller Detail

The Flow Controller has two functions. The first is to enable the user to switch between Low and High flow modes via the use of the High/Low switch to modulate reverse flow. This is accomplished by providing two parallel flow paths through the Controller Line: one with a low resistance flow path and the other with a high resistance flow path. When the switch is on Low, the low resistance flow path is pinched off, requiring all the blood flow to go through the high resistance path. When the switch is set to High, both paths are open and the blood flows through both paths in parallel, which in combination form a low resistance flow path.

The second function of the Flow Controller is to momentarily block the flow of blood through the Controller Line via a Flow Stop Button. This button is spring-loaded to be normally open and is designed to be used during injection of contrast through the arterial sheath into the carotid vasculature. By shutting off the arteriovenous shunt flow line during contrast injection, the contrast solution is prevented from immediately filling the shunt line rather than entering the artery. The normally open configuration of the button prevents the user from neglecting to re-open the shunt line (and thereby re-establishing reverse flow) after a contrast injection.

5.4 Intended Use

The NOVIS Transcarotid Neuroprotection System (NPS) is intended to provide transcarotid vascular access and embolic protection for the introduction of diagnostic agents and therapeutic devices during treatment of acute ischemic stroke (large vessel occlusion in the anterior circulation) in patients with distal ICA, MCA M1, proximal MCA M2, single-vessel MCA M2, dominant MCA M2, or co-dominant MCA M2 occlusions, within 24 hours of time last known well. Appropriate patients will have undergone a failed transfemoral attempt (as defined in Appendix 4) and have appropriate anatomy described below:

- Adequate femoral venous access as assessed by ultrasound
- Common carotid artery reference diameter of at least 6 mm

The NOVIS Transcarotid Neuroprotection System (NPS) is contraindicated for use in patients with significant disease of the ipsilateral common carotid artery.

The benefits and risks of carotid stenting in AIS patients have not been investigated, thus carotid stenting is not allowed in the NITE 1 Study.

6 Study Design

The NITE 1 Study is a prospective, single arm, multi-center feasibility study for the treatment of patients experiencing an acute ischemic anterior circulation stroke due to large vessel embolic occlusions of the intracranial ICA, MCA M1, proximal MCA M2, single-vessel MCA M2, dominant MCA M2, or co-dominant MCA M2 segments using the open-surgical transcarotid approach. The NOVIS Transcarotid NPS will be used to facilitate the transcarotid approach in patients that have failed transfemoral therapy.

7 Outcomes

7.1 Primary Outcomes

The following primary endpoints will be collected and evaluated in all enrolled patients:

- Device-related Serious Adverse Events – vascular complications including dissection, pseudoaneurysm, hematoma, arteriovenous fistula, thrombus formation, embolization and any vascular complication that may be attributed to the device AND requires surgical repair, surgical wound revision, transfusion, etc.
- Other Serious Adverse Events – permanent cranial nerve injury, new symptomatic ipsilateral hemorrhage and dissections related to ancillary devices
- Functional independence at 90 days (proportion with mRS score 0-2)

7.2 Secondary Outcomes

The following secondary outcomes will be collected and evaluated in all enrolled patients:

- Carotid access time
  - Hospital arrival to neck incision
  - Neck incision to carotid exposure
  - Neck incision to carotid artery catheterization (includes securement of sheath)
  - Neck incision to femoral venous sheath access (includes securement of sheath)
  - Neck incision to initiation of reverse flow
- Time to final revascularization
  - Hospital arrival to OR
  - Last known well to final revascularization
  - Admission to final revascularization
  - OR to final revascularization
  - Cutdown to final revascularization
  - Arterial introduction of interventional tools to final revascularization
  - Total reverse flow time (CCA clamp to CCA unclamp)

- Device-related complications
- Neurologic assessment at 90 days (proportion of patients with a nondisabling or disabling stroke according to NIHSS)
- Technical success rate – Successful introduction of endovascular tools through the NOVIS Transcarotid NPS.
- Rates of revascularization success assessed by angiographic core lab (mTICI ≥ 2b)

8 Study Population

8.1 Selection of Patients

Prospective study patients' medical history will be reviewed for potential eligibility by an approved member of the site clinical research team. Once eligibility is established, the research team should review the study follow-up requirements with the patient or patient's legal authorized representative. Patients who will not be able to return to the study site for the required follow-up visits should not be considered for enrollment.

8.2 Patient Eligibility

Patients enrolled into this study will be comprised of male and female patients who have had an acute ischemic anterior circulation stroke due to large vessel embolic occlusion who are candidates for endovascular therapy and in whom transfemoral therapy has failed.

Patients must meet ALL the inclusion criteria to be considered for the study. If ANY of the exclusion criteria are met, the patient cannot be enrolled in this study.

8.3 Inclusion Criteria

1. Patients presenting with acute ischemic stroke of the anterior circulation with large vessel occlusions who are eligible for revascularization using endovascular therapies (stentrievers and/or aspiration devices)
2. Occlusion of the intracranial ICA, MCA M1, proximal MCA M2, single-vessel MCA M2, dominant MCA M2, or co-dominant MCA M2 segments
3. Patient has failed transfemoral therapy (see Appendix 4 for definition), and at least 15 minutes have elapsed from groin puncture
4. Patient must meet current NOVIS Transcarotid Neuroprotection labeling requirements
    a. Adequate femoral venous access as assessed by ultrasound
    b. CCA reference diameter of at least 6 mm
5. Patient is ≥ 18 years of age
6. Patient willing/able to return for protocol required follow up visits
7. Patient or patient's Legally Authorized Representative (LAR) has signed the study Informed Consent form
8. Imaging requirement for patients presenting within 6 to 24 hours from last known well:
    a. < 1/3 MCA territory involvement, as evidenced by CT
    b. Clinical Imaging Mismatch defined as one of the following on CTP:
        i. 0-20 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old)
        ii. 0-30 cc core infarct and NIHSS ≥ 10 (and age < 80 years old)
        iii. 31 cc to ≤ 50 cc core infarct and NIHSS ≥ 20 (and age <80 years old)

8.4 Exclusion Criteria

Each potential patient must be screened to ensure they do not meet any of the following exclusion criteria. This screening is based on known medical history and data available at the time of eligibility determination and enrollment.

1. Significant disease of the ipsilateral common carotid artery on routine CTA
2. Presence of a cervical ICA loop or other high-risk anatomical features of the ICA on routine CTA, that may preclude the use of the NOVIS NPS
3. Any active or recent hemorrhage within the past 30 days
4. Embolectomy contraindications
    a. Pre-stroke mRS ≥2
    b. NIHSS ≤ 5
    c. ASPECTS ≤ 5
5. IV tPA has been or is being administered
6. Last known well > 24 hours ago
7. Known history of severe head injury within past 90 days with residual neurological deficit, as determined by medical history
8. Patient has an isolated hemisphere, defined as intracranial circulation that is fed only by the ipsilateral internal carotid artery and may be detected on prior CTA
9. Known history of neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g., dementia with prescribed anti-cholinesterase inhibitor (e.g., Aricept)
10. Presumed septic embolus, suspicion of bacterial endocarditis or cerebral vasculitis
11. Known history of ipsilateral severe intracranial atherosclerotic disease (≥ 70% stenosis) documented on prior imaging
12. Patient is known to have an active COVID-19 infection
13. Female who is pregnant or lactating at time of admission
14. Current participation in another investigational drug or device study.
15. Evidence of any other disease or condition expected to compromise survival or ability to complete the endovascular procedure or follow-up assessments during the 90-day follow-up period (e.g. methamphetamine, cocaine, or other recreational drug use)
16. Patient has recurrent or metastatic malignancy or cancer
17. Known history of hemorrhagic diathesis or coagulation factor deficiency
18. Known risks for paradoxical embolism, including intracardiac right-to left shunt (e.g., PFO, ASD, VSD) or history of pulmonary embolism or deep vein thrombosis
19. Patients that have undergone a transradial or transbrachial mechanical thrombectomy attempt prior to enrollment

9 Patient Enrollment

A patient is considered enrolled after:

1) written informed consent is obtained,

2) meeting all inclusion and none of the exclusion criteria,

3) failed transfemoral therapy

Patients who are screened but do not meet all study criteria are considered screen failures and will not be enrolled and no further follow-up assessments will be conducted.

9.1 Patient numbering

Patients will be identified by a Patient Identification (ID) number, which is a combination of the specified site number and a sequential number assigned by the site. The Patient ID will consist of a 3-digit number and will be consecutively assigned upon enrollment in the study.

9.2 Patient discontinuation

Where possible, every effort should be made for a patient to remain in the study until completion of the required follow-up period. However, if needed the patient's participation in the study may be discontinued at any time during the study. If this occurs, the reason for discontinuation should be documented in the source documentation, and the appropriate Case Report Form (CRF) must be completed. Factors leading to patient discontinuation may include, but are not limited to the following:

- **Patient Withdrawal**: Patient participation in a clinical trial is voluntary and the patient may discontinue participation (refuse all subsequent testing and follow-up) or withdraw their consent from the study at any time without affecting their future medical treatment or benefits.
- **Investigator Termination**: The Investigator may terminate the patient's participation without regard to the patient's consent if the Investigator believes it is medically necessary.
- **Lost to Follow-up**: A patient will be considered lost to follow-up after three unsuccessful, documented attempts have been made to contact the patient.
- **Death of Patient**: Upon notification of the death of the patient, the study site will be responsible for notifying Sponsor within 24 hours (refer to Section 12.2):

10 Study Procedures

10.1 Informed Consent

Prior to patient participation in this study, the Investigator will obtain written Institutional Review Board (IRB) approval for the protocol and the informed consent form (ICF). The approved consent form should clearly reflect the IRB approval date and protocol version.

Written informed consent must be obtained for all patients who are screened and meet the general inclusion/exclusion criteria prior to enrollment. The patient or the patient's Legally Authorized Representative (as defined by the local IRB) will be asked to sign the informed consent form before any study-specific tests or procedures are performed. A copy of the signed and dated informed consent will be provided to the study patient and/or the Legally Authorized Representative (LAR).

The nature and scope of the study, potential risks and benefits of participation, any questions the patient and/or the LAR may have, are to be addressed by the Investigator or person designated by the Investigator who has been trained to the study protocol. The study will be explained to the study patient and/or the LAR in lay terms and native language. Study patients will be assured that they may withdraw from the study at any time and for any reason. Trained study staff should

explain that even if a patient agrees to participate in the study and signs an Informed Consent Form, noninvasive baseline imaging or cerebral angiography may demonstrate that the patient is not a suitable candidate for the study treatment.

A Screening and Enrollment Log will be maintained by the site to document basic information such as date screened and reason for screen failures for patients who fail to meet the study eligibility criteria. Screen failed subjects will not be entered into the electronic database or followed beyond the screening visit, and no further data will be collected/recorded.

10.2 Pre-Procedure

All patients will undergo imaging assessments, neurological evaluation, and review of his/her medical history to determine eligibility. If any of these tests do not fall within the Investigator's standard clinical practice, they should still be conducted for patients to be enrolled in the study.

The neurological assessment will include a pre-stroke mRS and a baseline NIH Stroke Scale (NIHSS).

10.2.1 Pre-Procedure Imaging

The suitability of the common carotid artery for direct access (as part of standard of care) must be measured by computerized axial tomography (CT) angiography of both head and neck in accordance with the product labeling.

A CT-Perfusion study (CTP) will also be completed to ensure imaging requirements for inclusion criteria are met (Section 8.3). The CTP imaging and report will be submitted by the sites for core lab and DSMB review.

10.3 Transcarotid Endovascular Therapy Procedure

10.3.1 Intra-Procedural Medications

All medications will be administered per institution standard of care for endovascular therapy procedures. All medications administered should be recorded on the patient's medical record. Pertinent medication given to the patient will be recorded on the Concomitant Medication Form, with clear indication to the procedural step at which the medication was administered, as applicable.

10.3.2 Failed Transfemoral Therapy

For the purposes of this study, failed transfemoral therapy is defined as either a unsuccessful transfemoral mechanical thrombectomy attempt made for at least 15 minutes having elapsed from groin puncture or inadequate or prohibitive anatomy deems a transfemoral approach not possible, as determined by the operator (see Appendix 4 for definition).

Reasons for failed transfemoral therapy should be documented both on the patient's medical record and study CRFs.

10.3.3 Establishment of Transcarotid Flow Reversal

The type of anesthesia used during the procedure is left to the discretion of the Investigator and will be documented on the CRFs. Should the investigator choose to start with moderate sedation conversion to general anesthetic should only occur if the Investigator deems it necessary. The type of anesthesia used will be documented in the CRFs.

After completing confirmatory duplex ultrasound, access to the common carotid artery cephalad to the clavicle will be gained using surgical techniques.

Investigators are to follow the NOVIS Transcarotid Neuroprotection System (NPS) Instructions for Use (IFU) for setting up and establishing the reverse flow circuit. Upon placement of the NOVIS system and prior to clamping the CCA, the differential in pressure causes some blood to flow between the CCA and femoral vein. At this point, there is still some antegrade flow in the CCA and therefore the carotid and cerebral vasculature is not "protected". Once the CCA is clamped below the arterial sheath of the system on the Low flow setting, the NPS should remain on Low flow setting and switch to High flow upon the introduction of interventional tools through the completion of the procedure. Upon initial set-up of the device a pressurized, heparinized saline drip is connected to the 3-way stopcock on the side arm of the rotating hemostasis valve.

Any adverse events that are observed after establishing reverse flow will be followed through study exit.

10.3.4 Endovascular Therapy

Patients will be treated with endovascular therapy system(s) (stentrievers and/or aspiration catheters) currently cleared by the FDA, under their cleared indications for use, for thrombus removal in patients experiencing an acute ischemic stroke in the anterior circulation due to large vessel occlusion. Investigators will be trained to follow the published instructions for use for the endovascular therapy system used in the procedure. Deviations from the cleared time of usage must be documented as a protocol deviation. Ensure the neurointerventional devices are labeled with an outer diameter that is compatible with the inner diameter of the NOVIS NPS Arterial Sheath and attached rotating hemostasis valve.

These devices will be introduced into the vasculature via the NOVIS NPS Arterial Sheath, during this interventional step the NOVIS NPS will be set to High Flow and remain on this setting until the neurothrombectomy has been completed.

Once the endovascular therapy systems are introduced into the NOVIS NPS Arterial Sheath continuous reverse flow will be maintained throughout the interventional steps, until all other devices are removed and the thrombectomy attempt is complete.

The transcarotid intervention may be abandoned at the discretion of the treating operator. The operator will document reason for failure in patient records and study case report forms.

10.3.5 Procedural Angiography

Angiographic evaluations will be performed pre-procedure, after recanalization, and post procedure to determine level of revascularization. Angiography must be performed in the involved territory.

Prior to the start of the procedure, the mTICI scores within the vascular territory being treated should be assessed. Angiographic films of the occlusion being treated must allow clear visualization of the target artery. The same orientation should be used before and after endovascular therapy in order to allow a valid analysis of the reperfusion status of the vessel(s). These angiographic evaluations will be submitted by the sites for core lab review.

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

10.4 Post-Procedure Medications

Post-procedural medication should be administered per the institution's standard of care for endovascular therapy and should be documented on the Concomitant Medication Form.

10.5 Post-Procedure Surgical Wound Management

Surgical wound closure and management should be done per the institutional standard of care. Any significant post-procedural adverse event should be assessed and documented on the Adverse Event CRF.

11 Post-Procedure Evaluations

All enrolled patients will undergo MRI post-procedurally per the institutional standard of care. Post-procedural MRI imaging and reports will be submitted to Sponsor.

11.1 24 Hours Post-op

The NIHSS must be obtained within 24 hours (+/- 6 hours) from the end of the index procedure. This test must be performed whether or not it is considered part of the Investigator's standard of care and must be performed by neurologist or NIHSS-certified personnel. Every attempt should be made to have the same person conduct the exam at each follow-up visit. This assessor should be independent of the treating operator and patient's mechanical neurothrombectomy procedures. The primary operator of the treated patient may not perform the neurological exam.

Additionally, patients will undergo CT/CTA and CTP, per the Institution's standard of care at 24 hours to assess infarct volume, recanalization, hemorrhage, and reperfusion. The CTP imaging and report will be submitted by the sites for core lab and DSMB review.

For the 24 hours post-op time period, any changes to the patient's study medications are to be recorded from end of the index procedure up to 24 hours post-op. All Adverse Events occurring from the end of the index procedure to 24 hours post-op are to be reported. In the case of a suspected neurological event, NIHSS should be repeated as close to and prior to the 24th hour of symptom onset.

In the event of patient death prior to the 24-hour assessment, all available information regarding the primary cause of death and date/time of death will be reported. Additionally, site will report if the patient had "do not resuscitate" (DNR) or "comfort care only" status prior to expiration. All deaths must be reported to Sponsor within 24 hours of becoming aware (as per section 12).

11.2 Day 5-7 or Discharge

The patient may be discharged from the hospital when clinically stable, at the Investigator's discretion. The following neurological assessments must be obtained between Day 5-7 (if patient remains in hospital) or prior to discharge, whichever is earlier:

- NIH Stroke Scale
- Modified Rankin Scale

The neurological assessment must be performed whether or not it is considered part of the Investigator's standard of care and must be performed by neurologist or NIHSS-certified personnel. Every attempt should be made to have the same person conduct the exam at each follow-up visit. This assessor should be independent of the treating operator and patient's mechanical neurothrombectomy procedures. The primary operator of the treated patient may not perform the neurological exam.

Records of any changes to the patient's study medications are to be recorded from the 24-hour post-op visit up to discharge. All Adverse Events occurring from the 24-hour post-op visit to patient discharge are to be reported. In the case of a suspected neurological event, NIHSS should be repeated as close to and prior to the 24th hour of symptom onset.

In the event of patient death prior to the 5-7 day or discharge assessment, all available information regarding the primary cause of death and date/time of death will be reported. Additionally, site will report if the patient had "do not resuscitate" (DNR) or "comfort care only" status prior to expiration. All deaths must be reported to Sponsor within 24 hours of becoming aware (as per section 12).

11.3 Clinical Follow-up

Trained study staff at each site will review the study requirements with the patient to maximize compliance with the follow-up schedule. The trained study staff will instruct patient to return for follow-up assessments according to the study schedule of events listed in Appendix 1.

11.3.1 30 Days

The following neurological assessments must be obtained 30 days (+/- 7 days) from the index procedure:

- NIH Stroke Scale (required only for in office visits)
- Modified Rankin Scale

This visit may be completed via phone or in office visit. If a phone visit is administered, then the NIHSS will not be completed. If an in-office visit is completed both the NIHSS and mRS assessments should be completed. This visit and associated neurological assessments must be performed whether or not they are considered part of the Investigator's standard of care and must be performed by neurologist or NIHSS-certified personnel. Every attempt should be made to have the same person conduct the exam at each follow-up visit. This assessor should be independent of the treating operator and patient's mechanical neurothrombectomy procedures. The primary operator of the treated patient may not perform the neurological exam.

Records of any changes to the patient's study medications are to be recorded from discharge up to the 30-day follow-up visit. All Adverse Events occurring from discharge to the 30-day follow-up visit are to be reported. In the case of a suspected neurological event, NIHSS should be repeated as close to and prior to 24th hour of symptom onset.

In the event of patient death prior to the 30-day assessment, all available information regarding the primary cause of death and date/time of death will be reported. Additionally, site will report if the patient had "do not resuscitate" (DNR) or "comfort care only" status prior to expiration. All deaths must be reported to Sponsor within 24 hours of becoming aware (as per section 12).

11.3.2 90 Days

The following neurological assessments must be obtained 90 days (+/- 14 days) from the index procedure:

- NIH Stroke Scale
- Modified Rankin Scale

This visit is expected to be completed as an in-office visit. The neurological assessment must be performed whether or not it is considered part of the Investigator's standard of care and must be performed by neurologist or NIHSS-certified personnel. Every attempt should be made to have the same person conduct the exam at each follow-up visit. This assessor should be independent of the treating operator and the patient's mechanical neurothrombectomy procedures. The primary operator of the treated patient may not perform the neurological exam.

Records of any changes to the patient's study medications are to be recorded from the 30-day follow-up call/visit up to the 90-day follow-up visit. All Adverse Events occurring from the 30-day follow-up call/visit to the 90-day follow-up visit are to be reported. In the case of a suspected neurological event, NIHSS should be repeated as close to and prior to 24th hour of symptom onset.

In the event of patient death prior to the 90-day assessment, all available information regarding the primary cause of death and date/time of death will be reported. Additionally, site will report if the patient had "do not resuscitate" (DNR) or "comfort care only" status prior to expiration. All deaths must be reported to Sponsor within 24 hours of becoming aware (as per section 12).

If the COVID-19 Pandemic impacts the ability of the patient or site to complete this visit on-site, a remote phone visit may be done. If a phone visit is administered, then the NIHSS will not be completed.

11.4 Patient Flow Diagram

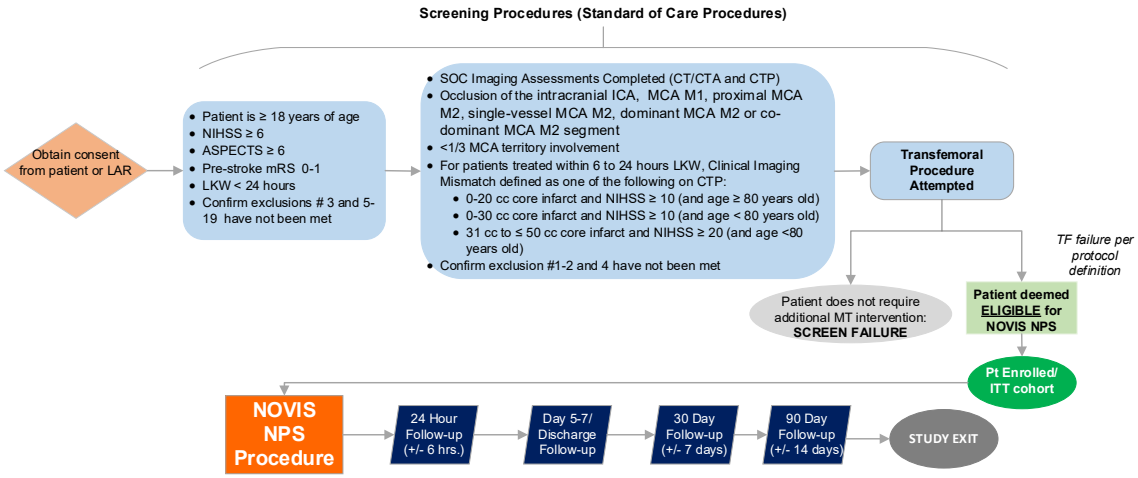


Image also provided in Appendix 5.

12 Adverse Events

Adverse event (AE) data will be collected and recorded from index procedure through 90-day follow-up period (or until patient discontinuation) for all enrolled patients on the Adverse Event CRF. At each evaluation, the Investigator or coordinator will determine whether an adverse event has occurred based on, but not limited to reports from the study patient, observed by the investigator or coordinator or documented in the medical record. For the purpose of this protocol, an adverse event is any untoward medical occurrence in a study patient, which may or may not have a causal relationship with the study device. It includes any pre-existing condition that increases in severity or frequency or any new events that occur after the index procedure. An elective procedure for a pre-existing condition (that has not worsened) is not considered an AE.

Event, date of onset, duration, severity, seriousness, treatment, outcome and relationship to the device or procedure will be recorded on the Adverse Event CRF and cross-tabulated according to:

- Severity (Mild, Moderate, Severe)
- Seriousness (Serious Adverse Event (SAE), Non-serious AE)
- Serious Adverse Device Effect (SADE)
- Unanticipated Adverse Device Effect (UADE)
- Procedure-Relatedness (Not Related, Possibly Related, Probably Related, Causal/Related)
- Device-Relatedness (Not Related, Possibly Related, Probably Related, Causal/Related)

Anticipated AEs have been listed in Section 23.1, 23.2, 23.3 & 23.4, and all AEs will be monitored until they are adequately resolved or explained at the end of the study follow-up period. Beyond the routine annual reports, interim progress report will be provided every three months to FDA.

12.1 Severity

The term “severe” is used to describe intensity (severity) of a specific event. An event itself, may be of relatively minor medical significance (such as a severe headache). This is not the same as a “serious”, which is based on an outcome usually associated with events that pose a threat to the subject’s life or functioning. (See Section 12.2 for definition of a serious adverse event.)

12.2 Serious Adverse Events

When an adverse event meets the definition for serious adverse event, it should be considered as such and reported immediately (within 24 hours) of becoming aware of the event to the Sponsor and recorded in the source documentation. The SAE should be further reported to the reviewing IRB per hospital IRB requirements. An adverse event is considered serious if the event:

- Leads to death;
- Leads to a serious deterioration in the health of the patient that:
  - Results in life-threatening illness or injury;
  - Results in permanent impairment of a body structure or a body function;
  - Requires inpatient hospitalization or prolongation of existing hospitalization;
  - Results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

An Adverse Event form will be completed promptly and no later than 10 working days after becoming aware of the event. Reports relating to the patient’s subsequent medical course must be submitted to the Sponsor and the reviewing IRB until the event has subsided or, in case of permanent impairment, until the event has stabilized, and the overall clinical outcome has been ascertained.

12.3 Serious Adverse Device Event

Serious adverse device events are defined as a device related AEs that has resulted in any of the consequences characteristic of a serious adverse event. The Investigator will report these events within 24 hours of becoming aware of the event to the Sponsor and to the reviewing IRB per hospital IRB requirements.

Reports relating to the patient’s subsequent medical course must be submitted to the Sponsor and the reviewing IRB until the event has subsided or, in case of permanent impairment, until the event has stabilized, and the overall clinical outcome has been ascertained.

12.4 Unanticipated Adverse Device Effects

Unanticipated adverse device effects are defined as any serious adverse effect on health, safety or any life-threatening problem or death caused by, or associated with the study device; if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the study protocol and informed consent. When an adverse event meets the definition of an unanticipated adverse device effect (UADE) or that relationship is unknown, the Investigator will report the event to the Sponsor within 24 hours and provide documentation within 10 working days after the Investigator first learns of the effect and to the reviewing IRB as required.

Follow-up reports relating to the patient's subsequent medical course must be submitted to the Sponsor and the reviewing IRB until the event has subsided or, in case of permanent impairment, until the patient's condition stabilizes, and the likely overall clinical outcome has been ascertained.

12.5 Relatedness

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized by the site Investigator. During causality assessment activity, clinical judgement shall be used, and the protocol consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered by the Investigator. Causality assessment will also be reviewed and adjudicated by the Clinical Events Committee.

Each AE will be classified according to four different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the adverse event to the investigational medical device or procedures:

- **Not Related**: The adverse event is determined to be solely caused by the underlying disease, disorder or condition of the study patient, or attributable solely to other extraneous causes (unrelated to the device, device malfunction or procedure).
- **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 where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
- **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
- **Causal / Related:** The adverse event is clearly caused by the use of the device, device malfunction or the procedure, as confirmed by: the event is recognized as a known event associated with the device or procedure, the event has a temporal relationship to device or procedure, the event involves the body site or organ the device or procedure is applied to or has an effect on, or event is related error in use.

12.6 Device Failures, Malfunctions and Nonconformities

All investigational device failures, malfunctions, and product nonconformities will be documented on the appropriate CRF and the involved device(s) should be returned to the Sponsor for analysis, if possible. Instructions for returning the investigational device(s) will be provided to the study sites in their Study binder. Device failures and malfunctions should also be documented in the subject's medical record. All investigational device failures, malfunctions, and product nonconformities shall be reported within 24 hours of becoming aware to the Sponsor.

All device malfunctions and nonconformities related to the interventional mechanical thrombectomy devices used in the procedure also should be reported in the CRFs.

13 Safety Monitoring

13.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review the safety data, including reportable adverse events. The DSMB will be empowered to recommend suspension of enrollment or termination of the study based on safety concerns. Based on their analysis, the DSMB may recommend that the sponsor modify or stop the study. Every effort will be made to allow the DSMB to complete an unbiased review of internal and external scientific factors relevant to the safety of the patient populations and the conduct of the study. The DSMB will be composed of a multi-disciplinary group of physicians and a statistician. The committee members will not be participating in the study and will not have an affiliation with the Sponsor, Investigators, Investigational sites, or core laboratories. Names of the members will not be announced but will be provided by the sponsor to the appropriate regulatory agencies upon request. The DSMB chairperson will notify the sponsor of any safety or compliance issues throughout the course of the study. The committee will also provide confidential recommendations, when necessary, of study termination based on safety stopping rules determined at the study onset, or because a clinically significant result or trend was identified in safety analyses of data. All DSMB reports will remain strictly confidential but will be made available to the appropriate regulatory agencies upon request.

During the course of the study, the DSMB will review accumulating safety data to monitor the incidence of Adverse Events and other trends that would warrant modification or termination of the study. The DSMB will meet at pre-specified intervals to assess the data against the prespecified safety and efficacy stopping rule as described within the DSMB Charter. In addition to the pre-specified meetings, the DSMB will meet for any other safety concerns that might arise during the active enrollment phase of the study. In addition, a designated member of the DSMB will be sent SAE data at regular time intervals, independent from the pre-planned DSMB meeting schedule. Data will be supplied to, and reviewed by, the DSMB as tables and/or listings. After review of the aggregate data, the DSMB may request additional information. The DSMB can also consider external data when appropriate, (e.g., published articles). Any DSMB recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Sponsor for consideration and final decision. However, if the DSMB at any time determines that a potential serious risk exists to subjects in this study, the DSMB chairman will immediately notify the Sponsor. The composition, guiding policies, operating procedures and stopping rules (if safety concerns arise during the review of the study data) will be described in the DSMB Charter.

13.2 Clinical Events Committee (CEC)

An independent Clinical Events Committee will be assembled to review and adjudicate all potential endpoint events and their relationship to the device or procedure that occur while a patient is enrolled in the trial. The committee will be comprised of a multidisciplinary group of physicians including at least one neurointerventionalist and at least one cardiologist. The committee members will not be participating in the trial and will not have an affiliation with the Sponsor, Investigators or Investigational sites. The composition, guiding policies and operating procedures will be described in the CEC Charter.

13.3 Core Lab

A central imaging core lab will be established to independently review angiographic and CTP imaging. Angiographic images will be reviewed to provide an independent assessment of the secondary efficacy endpoint of mTICI reperfusion scores at post procedure. CTP images obtained at baseline and at 24 (+/- 6) hours will be reviewed to determine volume of infarct and mismatch for DSMB assessment.

Instructions for standardized imaging and transfer will be provided to site by Sponsor. An imaging core lab charter will ensure that consistent policies and procedures are applied throughout the imaging core lab review and determination process, and will include a minimum of two core lab members. If an unresolvable disagreement is encountered, then a third member may be included or an alternative method may be used as needed.

For each enrolled subject, all images must be appropriately de-identified and submitted for core lab review. It is important that the images be saved in native DICOM format, and that all imaging sequences are sent (without pre-selecting specific frames). It is also important that the imaging sequences are captured chronologically and are clearly labeled with date and time stamps so that they can be correlated to pre-procedure, after recanalization, and post-procedure time points.

14 Statistical Methods and Sample Size

14.1 Populations for Analysis

The Intent-to-Treat (ITT) population is defined as patients who are enrolled as discussed in Section 9 who have consented (only once prior to screening), who meet all inclusion and none of the exclusion criteria , and in whom transfemoral therapy has been deemed a failure.

The per protocol (PP) population will be comprised of patients from the ITT population AND for whom no major protocol deviations have occurred.

14.2 Sample Size

A minimum of 30 and a maximum of 40 patients will be enrolled into the PP population and analyzed in this study. Enrollment in the ITT cohort will cease when 30 PP patients have been accrued. Additional patients beyond 30 who are successfully enrolled while waiting for the 30th PP patient to complete the 90-day follow-up period, will be analyzed in the cohort for which they qualify, whether PP or ITT. Enrollment will continue till a maximum of 60 patients are enrolled in the ITT population or the DSMB stops the study for safety reasons.

14.3 Endpoint Analyses and Hypothesis Testing

No formal statistical hypothesis will be tested because this is a feasibility study with a small sample size. Serious Adverse Events will be tabulated and reported accordingly.

The primary endpoint and all secondary endpoints will be analyzed based on both the ITT and PP population. All available data on the ITT patients who enrolled in the study will be included.

15 Data Collection

Data will be entered into a validated electronic data management system using standardized electronic Case Report Forms (eCRFs). All efforts should be made by the Investigator and trained study staff to complete the eCRFs in their entirety. This includes all data regarding adverse events, protocol deviations, patients lost to follow-up, and other relevant data.

15.1 Required Data

For the duration of the study, the Investigator will maintain complete and accurate documentation, including but not limited to, medical records, study progress notes, laboratory reports, CRFs, signed patient informed consent forms, device accountability logs, correspondence with the reviewing IRB, sponsor and Study Monitor, adverse event reports, and information regarding patient discontinuation or completion of the study.

The Investigator/institution will permit direct access to source data and documents for study-related monitoring, audits, IRB reviews, event adjudication and regulatory inspections to be performed. The Investigator will obtain, as part of the informed consent process, permission for authorized sponsor employees, study monitors or regulatory authorities to review, in confidence, any medical records that concern patients in this trial, whether or not they contain personally identifying information.

15.2 Source Documentation

Regulations require that the Investigator maintain information in the patient's medical records, which corroborate data collected for the study. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained:

- Medical history / general physical condition of the patient before involvement in the study of an enough nature to verify the protocol eligibility criteria.
- Dated and signed study/progress notes on the date of entry into the study documenting the following:
    - the general health of the patient,
    - completion of the informed consent process
- Dated and signed notes from each patient visit to support all data recorded on the CRFs.
- Adverse events reported and their continuation or resolution at EACH visit, including supporting documents such as discharge summaries, catheterization lab reports, lab results, CT/MRI reports.
- Notes regarding prescribed medications taken during the study (including start and stop dates if known).
- Patient's general health and medical condition upon completion of, or withdrawal from, the study.

15.3 Record Retention

The Investigator will maintain all essential documents and source documentation (patient medical records) that support the data collected on the enrolled patients in compliance with ICH/GCP guidelines. Documents must be retained for at least two years after (1) study completion following the FDA or other regulatory approval, or (2) the study has been terminated by the Sponsor. Documents must be retained until Silk Road Medical (SRM) informs the Investigator that study documentation no longer needs to be maintained. The participating physician will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If the participating physician withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility, written notification sent to Sponsor who will notify FDA.

15.4 Confidentiality

All data and information collected during this study will be considered confidential by the Sponsor. All data used in the analysis and summary of this study will be presented while protecting individual patient health information (PHI). Access to patient files will be limited to authorized personnel of the Sponsor, the Investigator, Clinical site research staff and authorized Regulatory Authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study.

15.5 Release of Data/ ClinicalTrials.gov

For applicable clinical trials that are subject to 42 CFR 11.42, the standard submission deadline for study results on ClinicalTrials.gov is no later than 1 year after the study's Primary Completion Date, as described in 42 CFR 11.44(a) of the final rule.

16 Site Responsibilities

16.1 Investigator Responsibilities

The Investigator is responsible for ensuring that the clinical study is conducted according to this Clinical Protocol, and all conditions of IRB approval and applicable regulations. Written confirmation of IRB approval must be provided to SRM prior to the enrollment of any patient in the clinical study. The Investigator is responsible for ensuring Informed Consent is obtained from all patients prior to any diagnostic tests or treatments outside of the standard course of treatment if this patient were not considered for enrollment in this clinical study.

Patients must be informed that their medical records will be subject to review by the Sponsor, its authorized designee, or local regulatory representatives. Patients will be informed that they are free to refuse to participate in this clinical study without loss of benefits to which they are otherwise entitled, and if they choose to participate, they may withdraw at any time without prejudice to future care. The informed consent approved by the respective clinical sites' IRB must be signed prior to study participation. The original signed informed consent for each patient must be retained by the Investigator and is subject to review by Sponsor and the local regulatory authorities.

17 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of the study devices. Device Accountability Logs supplied by the sponsor, must be completed for each study device. The disposition of all devices must be documented, including those that have been discarded and those returned to the sponsor. Devices that are not associated with use for a study patient should only be identified with a patient number (for example, devices that are inadvertently contaminated during a case). When the enrollment phase of the study is complete, the Investigator will return to the sponsor any unused devices and a copy of the completed Device Accountability Logs.

Use of the device outside of this study protocol is strictly forbidden and will constitute grounds for removal of the Investigator and/or institution from the study.

17.1 Device Returns

All investigational devices that are required to be returned to the Sponsor will use the sponsor's Return Materials Authorization (RMA) procedures that are outlined in the Study Manual. These devices may include the following:

- All unused study devices when enrollment is complete
- All study devices associated with a device malfunction or failure
- All opened but unused study devices that may be contaminated, have a defect in the sterile barrier prior to use, or have some other potential defect that was identified
- All expired study devices.

Study devices that were opened in error, prepped incorrectly or contaminated in the lab, for instance dropped on the floor, do not need to be returned to the sponsor.

18 Sponsor Responsibilities

Prior to shipping product, the Sponsor is responsible for selecting Investigators and obtaining and reviewing copies of appropriate IRB approvals. It is the sponsor's responsibility to ensure that the study is conducted according to Good Clinical Practice (GCP), applicable regulatory requirements, the Study Protocol, and any additional conditions that are indicated or mandated by the IRB at each site, or regulatory authorities. Additionally, the sponsor will ensure proper training of the site and sponsor personnel, regular monitoring of the study, and ensure that Informed patient consent is obtained for each study patient prior to the completion of the index procedures.

18.1 Selection of Clinical Investigators and Sites

The sponsor will select Investigators approved by training and experience in participating in clinical trials. Up to 8 US will be recruited and selected based upon a site assessment, appropriate facilities, and the qualifications of the Primary 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. Additional selection criteria may be applied in site and/or Investigator selection:

- Adequate study population to meet the requirements of the study
- Adequate time to be personally involved in the conduct of the study
- Adequate research staff and resources to support the study
- Experience in conducting studies
- Appropriate OR (hybrid or otherwise) permitting transfemoral and surgical approaches to be performed without moving the patient within the hospital
- Investigators must be individual(s) experienced with endovascular therapy AND Investigator must be a Neurosurgeon
- Investigator must be TCAR trained
- Investigator must currently perform or have hospital privileges to perform CEA.
- The facility must be certified as a Comprehensive Stroke Center through an accredited organization.
- Willingness to observe confidentiality at all times
- Compliance to protocol procedures and willingness provide Sponsor with accurate performance data in a timely fashion
- The facility must be associated with an Institutional Review Board (IRB) that satisfies all applicable regulatory requirements and conducts meetings on a regular basis.

Prior to enrolling patients, each potential Investigator must submit a current, signed and dated curriculum vitae, a completed financial disclosure form, a completed Investigator agreement and has completed Sponsor approved protocol training.

18.2 Training of Investigators and Site Personnel

The training of appropriate clinical site personnel will be the responsibility of the sponsor. Investigators and Site Personnel will be trained on the following aspects of the clinical study:

- Protocol
- Case Report Forms
- Risks and Benefits
- Reporting Responsibilities
- Informed Consent
- Device Usage
- Device Instructions for Use
- Confidentiality

19 Study Monitoring

The Sponsor or designee will regularly monitor the study throughout its duration. Study Monitors will visit each site at appropriate intervals to review clinical data for accuracy and completeness and to ensure compliance with the protocol. The Study Monitor may inspect all documents and records maintained by the Investigator, including medical records (office, clinic or hospital) for the enrolled patients in this study. The Investigator will facilitate access to these records by authorized representatives of the Sponsor, and appropriate regulatory agencies.

A study termination (close-out) monitoring visit will be conducted at the completion of the study to ensure that all clinical study materials and patient data are properly documented and stored until SRM informs the Investigator that data collection has been completed. The sponsor will notify each site during the closeout visit of the current data storage requirements.

If the Study Monitor becomes aware that an Investigator is not complying with the signed Investigator Agreement, the Study Protocol or any conditions of approval imposed by the reviewing IRB or regulatory authorities, the Sponsor will immediately either secure compliance, suspend enrollment at the site, or discontinue shipments of the device to the Investigator until compliance is achieved and guaranteed. The Sponsor may also terminate the Investigator's participation in the study. The Investigator will be required to return all unused devices to the Sponsor unless this action would jeopardize the rights, safety or welfare of a patient.

19.1 On-Site Audits

In accordance with FDA and Competent Authority regulations and the Sponsor's operating procedures, the Sponsor or designee may request access to all study records, including source documents, for inspection and duplication. In the event that an Investigator is contacted by a regulatory agency in relation to this study, the Investigator will notify the Sponsor immediately.

The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by an authorized regulatory representative during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. Sponsor will provide any needed assistance to regulatory audits or correspondence.

20 COVID-19

The mitigation and impact assessments listed in this section are meant as contingencies for occurrences of pandemic or endemic-like situations, as seen during the pandemic of 2020 due to COVID-19. Sponsor and investigative sites are not limited to the actions or mitigations listed in this section and may take additional steps to ensure patient safety and well-being.

20.1 ICF Process or Patient Impact

The study is designed to exclude patients who are known to be positive for COVID-19 at enrollment. The consenting guidelines laid out in section 10.1 should be maintained.

If an enrolled patient tests positive for COVID-19 during the study follow-up period (post-procedure and thereafter), the patient will be followed through study exit.

20.2 Visits/Procedures

A site's ability to conduct follow-up visits on-site may be impacted due to the pandemic. In these circumstances the site should make efforts to conduct e-visits (phone/ video based) within study visit windows. If e-visits are implemented, the site will ensure:

- Trained study staff conducting e-visits have been trained on how to conduct e-visits (e.g., training on the use of telemedicine applications).
- Procedures to maintain patient's privacy are in place, as would be done for an on-site clinical visit.
- Both the investigator and the trial participant should confirm their respective identities with one another before engaging in a real-time video conference visit according to an identity verification plan developed by the sponsor.

It is understood that the use of e-visits will limit the ability of trained study staff to complete all protocol required neurological assessments. The NIHSS will not be collected at these e-visits.

20.3 Protocol Deviations

Deviations from study visits and procedures caused by COVID-19 will be reported and collected in study case report forms under specified "COVID-19" categorizations.

20.4 AE Collection and Reporting

All reported events will be collected and reported in association to COVID-19 in the study case report forms.

20.5 On-site Monitoring

If the sponsor or sponsor representatives are unable to complete on-site monitoring visits due to COVID-19, the sponsor will attempt to utilize remote monitoring practices, where possible. The Sponsor will focus on trial activities that are essential to the safety of trial participants and/or data reliability. The details of these contingencies are laid out in the Monitoring Plan.

20.6 Study Personnel Turnover

In the case of Site Personnel change or turnover, all new personnel will be trained via teleconferencing by Sponsor. The extent of this training will be determined based on the role and delegated tasks new site personnel will be required to undertake.

21 Protocol Amendments

FDA approved protocol amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Investigator will be responsible for notifying the reviewing IRB of the protocol amendment (administrative changes) or obtaining IRB approval of the protocol amendment (changes in patient care or safety), according to the instructions provided with the

protocol amendment. The IRB acknowledgement/approval of the protocol amendment must be documented in writing prior to implementation and copies provided to the Sponsor.

22 Protocol Deviations

A protocol deviation is defined as an event in which the clinical Investigator or Trained Study Staff deviate from the study protocol or study procedures. A major protocol deviation is a deviation from the study protocol that affects the patient's rights, safety, or well-being. If the deviation meets any of the following criteria, it is considered a major protocol deviation:

- changing the protocol without prior IRB approval,
- failure to obtain informed consent, or
- falsifying research or medical records.

It is the Investigator's responsibility to ensure there are no deviations from the protocol and study conduct is in full compliance with all established procedures and conditions of the reviewing IRB. The Investigator will inform the sponsor of all deviations, and the reviewing IRB/EC of all protocol deviations as per the IRB/EC requirements for this study and confirm notification to the sponsor in writing. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of Investigator compliance to the protocol, Good Clinical Practice, and regulatory requirements.

Failure to obtain a signed informed consent form prior to the index procedure constitutes a major protocol deviation and non-compliance with internationally recognized good clinical practices per ISO 14155, the Declaration of Helsinki and the Code of Federal Regulations (21 CFR 50.20 General requirements for informed consent).

In the event that an Investigator does not comply with the Clinical study/Investigator agreement, and/or the protocol, the Investigator will be notified of their non-compliance, and the circumstances will be reviewed by the sponsor. Continued non-compliance may result in discontinued shipment of study devices and patient enrollment or termination of the Investigator's and/or investigational site's participation in the study.

23 Risk Benefit Analysis

23.1 CT Imaging

CT/CTA/CTP scans of the brain obtained at baseline and 24 hours post procedure are considered standard medical care. The risk associated with performing a CT/CTA/CTP scan is the ionizing radiation exposure. The radiation dose that is received is the same dose that would be received from standard clinical care to assess and treat the underlying medical condition. There is no additional risk of increased ionizing radiation exposure as a result of participation in this study.

A small amount of radiation is used to obtain a CT Angiogram (CTA). The radiation dose from this study is below the levels that are thought to result in a significant risk of harmful effect. There is some chance of an allergic reaction to the x-ray contrast (dye) used during the CTA.

Due to differences in standards of care between sites, it is possible that some patients may receive additional follow-up imaging or neurologic examinations other than those required by the protocol. The risks of these neurologic examinations are negligible, and the subject would likely benefit from enhanced care due to these additional tests.

23.2 Diagnostic Angiograms or Fluoroscopy

The risks associated with angiography are well documented and understood by the medical community. The arteriogram itself can cause problems with brain function and it can potentially make the subject's condition worse. Other risks related to the diagnostic angiographic procedure are relatively low but may include:

- Allergy to the contrast material
- Arteriovenous fistula formation
- Hemorrhage
- Death
- Dissection
- Distal embolization
- Hematoma
- Infection
- Neurological injury
- Pseudoaneurysm
- Thrombosis
- Vessel injury

Renal toxicity and idiosyncratic responses to the injected contrast medium including anaphylactic reactions have also been reported. Anticoagulation is not required during EVT for LVO in AIS in the NITE 1 protocol. It is unlikely that study patients are on DAPT and so the risk of bleeding is possible but unlikely. The risk of bleeding may be increased when diagnostic angiography is performed in individuals who are receiving anticoagulation and/or antiplatelet therapy. Neurological injury associated with these vascular complications may occur.

23.3 Risk Analysis for Endovascular Therapy

Endovascular therapy has known and well-defined risks, but some patients may be at greater risk as a result of existing co-morbidities. The Investigator will evaluate the risk to each patient on an individual basis and discuss the risks and benefits of study participation with each patient or legally authorized representative. This treatment may involve some additional risks to the patient, the nature of which are unknown. The following is a list of possible adverse events that may be attributable to the endovascular therapy procedure. These include, but are not limited to, the following:

- Access site complications
- Allergic Reaction
- Aneurysm perforation/rupture
- Air embolism
- Angina/coronary ischemia
- Arteriovenous Fistula
- Brain Edema
- Change in mental status
- Cranial nerve injury
- Death
- Device(s) deformation, collapse, fracture or malfunction
- Distal embolization including to a previously uninvolved territory
- Embolism
- Inflammation
- Ischemia
- Neurologic deterioration including stroke progression, stroke in new vascular territory, or death
- Pain
- Persistent neurological deficits
- Pseudo aneurysm formation
- Rupture
- Stroke
- Thrombosis
- Transient Ischemic Attack (TIA)
- Vessel dissection
- Vessel occlusion
- Vessel perforation

- Headache
- Hematoma
- Hemorrhage
- Infection
- Vessel rupture
- Vessel spasm

Risks and complications of endovascular therapy are also associated with the possible adverse events from fluoroscopy, which is routinely used in endovascular procedures. The probability of these adverse events increases as procedure time and the number of procedures increase. These risks include but are not limited to:

- Alopecia
- Burns ranging in severity from skin reddening to ulcers
- Cataracts
- Delayed neoplasia

23.4 Risk Analysis for Transcarotid Access with Reverse Flow

There exists a risk of access site complications associated with the surgical transcarotid access in this protocol, which is comparable to the risks associated with other routes of access used in mechanical thrombectomy procedures. These complications may include:

- Abrupt vessel closure
- Airway compromise
- Arteriovenous fistula
- Asphyxiation
- Cranial nerve injuries
- Hematoma
- Hemorrhage
- Infection/ sepsis
- Inflammation
- Pain and tenderness
- Pseudo aneurysm formation
- Vessel dissection
- Vessel occlusion
- Vessel perforation
- Vessel rupture
- Vessel spasm

Risks associated with the use of a proximal embolic protection device may include:

- Allergic reaction
- Aneurysm perforation
- Aneurysm rupture
- Angina/coronary ischemia
- Bacteremia/septicemia
- Bradycardia/arrhythmia and other conductions disturbances
- Cerebral edema
- Component Damage
- Congestive heart failure
- Death
- Deep vein thrombosis
- Deployment and retrieval failure
- Device(s) deformation, collapse, fracture or malfunction
- Distal embolization
- Distal embolization to a previously uninvolved territory
- Hyperperfusion syndrome
- Hypertension/ hypotension
- Ischemia/ infarction of tissue/ organ
- Ischemic stroke
- Myocardial infarction
- Neurologic deterioration including stroke progression or stroke in new vascular territory
- Persistent neurological deficits
- Pulmonary embolism
- Reduced blood flow
- Renal failure/insufficiency
- Seizure
- Stroke or other neurological complications (e.g., paralysis, paraplegia, or aphasia)
- Stroke in a contralateral hemisphere or brainstem (secondary to intracardiac right-to-left shunt)
- Thrombosis
- Thrombophlebitis

- Drug reactions
- Embolism (which includes thrombus, plaque, air, device and / or component)
- Fever
- Fluid overload
- Headache
- Hemorrhagic stroke
- Transient ischemic attack
- Ventricular fibrillation
- Unstable angina pectoris

23.5 Potential Benefits

Endovascular therapy remains the standard of care in the treatment of acute ischemic stroke caused by large vessel occlusions. The transcarotid approach provides a method of providing endovascular therapy even when standard transfemoral therapy options are no longer a viable or effective option.

The transcarotid approach will additionally provide a more direct access and visualization of the occlusion and may be impactful in reducing the time needed to engage and recanalize the occluded vessel. This approach will provide for a less tortuous environment for the delivery of the thrombectomy devices and may in turn yield a higher rate of first pass efficacy and reperfusion rates (mTICI 2b/3). In turn, these higher reperfusion rates may translate to better outcomes at 90 days post-procedure (mRS 0-2).

The transcarotid approach may also facilitate rapid exchange of endovascular therapy devices. This approach combined with the use of NOVIS NPS to establish flow reversal, augments the thrombectomy procedure and may potentially lower the rate of distal emboli or emboli in new territories. By directing emboli away from the brain, to the NOVIS NPS acts as a protection mechanism before initiating EVT.

23.6 Minimization of Risks

In order to mitigate the risks to the patient outlined above in Section 23.2 – 23.4, a variety of measures have been implemented into the study design to ensure patient safety.

The Sponsor will ensure that all Investigators will meet pre-specified criteria for Investigator selection and will successfully complete the mandatory device and protocol training provided by the Sponsor. All Investigators and Sites selected for this study have sufficient expertise and resources to manage any adverse events and conduct endovascular procedures. The Sites selected for the study are certified Comprehensive Stroke Centers to ensure necessary staff knowledge and appropriate equipment and resources. Participating investigators must be neurosurgeons who are also “TCAR trained”, which is a training and credentialing status that meets the requirements of the Society for Vascular Surgery (SVS) and represents the operator’s knowledge of performing the TCAR procedure using the ENROUTE NPS System, which is the predecessor to the NOVIS NPS. Additionally, the investigators must currently perform or have hospital privileges to perform CEA at the investigational site in the case that emergent surgical repair of the carotid artery becomes necessary.

The sample size of the study has been limited in size and to patients who have a failed transfemoral attempt, leaving no other thrombectomy therapy options other than the study procedure.

Sites must obtain IRB approval prior to screening and enrolling patients into the study. Signed Informed Consent will be required prior to participation, which will explain their treatment choices

and the risks and benefits of being in the study. CTP neurological imaging maps will be used to measure the core infarct volume and only those subjects who have small to moderate core infarct volumes will be enrolled into the trial. Sites will be provided with Instructions for Use for the NOVIS NPS being used. During the procedure the Investigators will pre-place sutures at the planned common carotid artery puncture site to provide rapid hemostasis upon arterial sheath retrieval, as outlined in the Instructions for Use. The artery and incision will be closed using standard surgical techniques and will be monitored post-operatively.

The Site will observe standard hospital procedures in the care of patients who undergo endovascular procedures. Frequent neurological and hemodynamic checks will be performed per standard hospital procedures during and post-procedure. Vital signs, particularly the patient's heart rate and blood pressure during and after the procedure will be monitored as standard of care, since rapid intervention must be undertaken to correct sudden changes in the patient's hemodynamic or neurologic status.

As part of this study protocol, the Investigator ensures all patients meet all enrollment criteria listed in Section 8 with particular adherence being made to ensure that the patient population consists of those that have undergone a failed transfemoral attempt (see Appendix 4 for definition).

Additional follow-up assessments at 30- and 90-day intervals are predesigned into the study to aid in monitoring patient safety and assessing any change in the patient's outcomes. The investigator will ensure the patient remains compliant with follow-up instructions and visits. The patients and their families will also receive the research teams contact information in case of an emergency or occurrence of an adverse event.

Safety monitoring of the data, consisting of individual event and aggregate data review, will be ongoing and conducted at a rate commensurate with patient enrollment in the trial. The DSMB will provide subject safety oversight and make recommendations to Sponsor regarding continuing enrollment, modifying, or stopping the study early based upon a review of the comparative rates of SAEs.

As a result of these risk mitigations, this study has been designed to demonstrate the potential benefits of the NOVIS Transcarotid NPS in the treatment of acute ischemic stroke caused by large vessel occlusions.

24 Non-Protocol Research

The Sponsor has a legal responsibility to the regulatory authorities to fully report all the results of sponsored clinical studies. No investigative procedures other than those in this protocol shall be undertaken on the enrolled patients without the PRIOR written approval of the reviewing IRB and the Sponsor.

25 Use of Information and Publication

All information and data generated in association with this study will be held in strict confidence according to local regulation and remains the sole property of Silk Road Medical, Inc. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the Sponsor.

At the conclusion of this study, a multi-center abstract reporting the primary results may be prepared and presented in an appropriate scientific forum. A multi-center peer-reviewed manuscript may also be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the study will be coordinated with the Sponsor. The site shall have the right to publish their individual results but only after publication of the multi-center publication is complete, provided, however, that at least sixty (60) days prior to the initial submission of a publication or presentation, the site provides Silk Road Medical with a copy of the publication or presentation for Silk Road Medical's review and approval, as referenced in the study Clinical Trial Agreement. Silk Road Medical reserves the right to delay approval either to prevent bias in ongoing clinical trials or to prevent adverse impact on the completion of the planned clinical program.

In accordance with 42 CFR Part 11, Sponsor will register this study on ClinicalTrials.gov and submit study results no later than 1 year after the primary completion date of the study or early termination date.

26 Study Termination

The Sponsor will monitor the progress of the study and the DSMB will monitor subject safety according to the DSMB charter. If warranted and as specified in the DSMB charter, the study may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population or inadequate patient enrollment. The sponsor takes responsibility for releasing any available outcomes in a reasonable and appropriate time frame on ClinicalTrials.gov.

Notification of suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the reviewing IRB, the appropriate regulatory agencies, and to all participating Investigators. A suspended or terminated study may not be reinitiated without PRIOR approval of the reviewing IRB and the study sponsor.

The Sponsor may terminate Investigator and site participation in the study if there is evidence of an Investigator's failure to maintain adequate clinical standards or evidence of an Investigator or trained study staff's failure to comply with the protocol, as described in Section 21.

Appendix 1. Schedule of Events

Procedure /Test	Pre-procedure	Procedure	Post-procedure		Follow-up Visits	
			24 hrs. (+/- 6 hrs.)	Day 5-7 / Discharge (whichever is earlier)	30 Day (+/- 7 days)	90 Day (+/- 14 days)
Patient Informed Consent	x					
Medical history	x					
Neurological Examinations						
NIH Stroke Scale	x		x[2]	x	x[3]	x
Modified Rankin Scale	x[1]			x	x	x
Imaging Assessments						
CT/CTA	x[4]		x[2]			
CTP	x		x			
Confirmatory DUS		x				
Angiography		x				
ASPECTS	x					
MRI			x			
Other Assessments						
Endovascular Therapy		x				
Concomitant Medications	x	x	x	x	x	x
Concomitant Therapies	x	x	x	x	x	x
Adverse Events		x	x	x	x	x

[1] Modified Rankin will be evaluated for pre-stroke disabilities.
[2] To determine presence of symptomatic cerebral hemorrhage.
[3] NIH Stroke Scale completed if visit is in-office
[4] CT/CTA at pre-procedure must be of head and neck

Appendix 2. Neurological Assessments/Scoring

Alberta stroke program early CT score (ASPECTS) (Pexman et al. 2001)

The Alberta stroke program early CT score (ASPECTS**)** is a 10-point quantitative topographic CT scan score used in patients with MCA strokes. Segmental assessment of the MCA vascular territory is made, and 1 point is deducted from the initial score of 10 for every region involved:

- caudate
- putamen
- internal capsule
- insular cortex
- M1: "anterior MCA cortex," corresponding to frontal operculum
- M2: "MCA cortex lateral to insular ribbon" corresponding to anterior temporal lobe
- M3: "posterior MCA cortex" corresponding to posterior temporal lobe
- M4: "anterior MCA territory immediately superior to M1"
- M5: "lateral MCA territory immediately superior to M2"
- M6: "posterior MCA territory immediately superior to M3"

Modified Rankin Scale (mRS)(Broderick et al. 2017)

The modified Rankin scale is used to qualify functional outcome in patient who suffer a neurological event. The scale comprises six levels, from 0 to 5, of increasingly severe disability where 0-2 is generally considered a good outcome with individuals assuming complete functional independence. The assessment should be made in a manner free of attribution to the incident stroke or the subject's condition prior to stroke.

- 0: no symptoms/normal
- 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

Modified TICI Scale (mTICI Scale)(Zaidat et al. 2013)

The modified thrombolysis in cerebral infarction (mTICI) grading is a tool for determining the response of thrombolytic therapy for ischemic stroke. In neurointerventional radiology it is commonly used for assessing patients post endovascular revascularization.

0: No Perfusion - No antegrade flow beyond the point of occlusion

1: Penetration with Minimal Perfusion - The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run

2: Partial Perfusion - The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction; However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction

2a: Only partial filling (< 50%) of the entire vascular territory is visualized

2b: Filling of > 50% all the expected vascular territory is visualized, but the filling is slower than normal

3: Complete Perfusion - Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

National Institutes of Health Stroke Scale (NIHSS)(Meyer et al. 2009)

The NIHSS is a graded neurological examination assessing consciousness, eye movements, visual fields, motor and sensory impairments, ataxia, speech, cognition and inattention. Often used to assess the severity of strokes based on the 11 components:

1. level of consciousness (1a: 0-3, 1b: 0-2 and 1c: 0-2)
2. best gaze (0-2)
3. visual fields (0-3)
4. facial palsy (0-3)
5. arm motor (0-4)
6. leg motor (0-4)
7. limb ataxia (0-2)
8. sensory (0-2)
9. best language (0-3)
10. dysarthria (0-2)
11. extinction and inattention (0-2)

These 11 components are then summed and the score correlates to stroke severity:

- 0 = no stroke symptoms
- 1-4 = minor stroke
- 5-15 = moderate stroke
- 16-20 = moderate to severe stroke
- 21-42 = severe stroke

Appendix 3. Abbreviations

Abbreviation	Term
ACA	Anterior Cerebral Artery
AE	Adverse Event
AHA	American Heart Association
AIS	Acute Ischemic Stroke
ASA	American Stoke Association
CCA	Common Carotid Artery
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computerized Tomography
CTA	Computerized Tomography Angiography
CTP	Computerized Tomography Perfusion
CV	Curriculum Vitae
CVA	Cerebral Vascular Accident
DE	Distal Embolization
DNR	Do Not Resuscitate
ECA	External Carotid Artery
ECG	Electrocardiogram
ENT	Embolization to New Territory
EVT	Endovascular Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IA	Intra-Arterial
ICA	Internal Carotid Artery
ICA-T	Internal Carotid Artery-Terminus
ICF	Informed Consent From
IFU	Instructions for Use
ID	Identification
IM	Intramuscular
Inc.	Incorporated
IRB	Institutional Review Board
ITT	Intent-To-Treat
IU	International Unit

Abbreviation	Term
IV	Intravenous
LAR	Legally Authorized Representative
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis in Cerebral Infarction
N/A	Not Applicable
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NPS	Neuroprotection System
PHI	Patient Health Information
PP	Per Protocol
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SICH	Symptomatic Intracranial Hemorrhage
TCAR	Transcarotid Artery Revascularization
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
tPA	Tissue Plasminogen Activator (alteplase)
UADE	Unanticipated Adverse Device Effect

Appendix 4. Definitions

Access Site Complication
Complication related to the vascular access site for the index procedure including but not limited to dissection, pseudoaneurysm, hematoma, arteriovenous fistula, thrombus formation, embolization and any vascular complication that may be attributed to the device AND that requires surgical repair, surgical wound revision, transfusion etc.

Adverse Event (AE)
Any unintended disease or injury or untoward clinical sign in a research patient.

CEA—Carotid Endarterectomy
A surgical procedure in which atherosclerotic plaque is removed from the diseased carotid artery.

CVA—Cerebral Vascular Accident *(See definition for Stroke)*

Death
Cessation of brain, cardiac, and pulmonary functions

Neurologic Death Death due to stroke or other neurologic cause.

Cardiac Death Death due to MI or other cardiac cause.

Other Death that cannot be attributed to neurologic or cardiac causes.

Device Malfunction
The failure of a device to meet any of its performance specifications or perform as intended. Performance specifications include all claims made in the labeling of the device.

Device Related Adverse Event
An Adverse Event that was directly caused by the study device (NOVIS NPS).

Distal Embolization (DE)
Embolization of pieces of the original thrombus “downstream” in the same vascular territory as the original thrombus.

Embolization to New Territory (ENT)
Any new infarct seen in the ipsilateral ACA for MCA occlusions, on CTA or MRI at the 24-hour time point compared to baseline CT or MRI.

Failed Transfemoral Therapy
Either a transfemoral mechanical thrombectomy attempt was made unsuccessfully with at least 15 minutes having elapsed from groin puncture, or there is inadequate or prohibitive anatomy deeming a transfemoral approach not possible, as determined by the operator.

Good Clinical Outcome
A measure of neurologic functional outcome with a score of 0–2 on the modified Rankin Scale (mRS), assessed at the 90-day follow-up visit.

Intracranial Hemorrhage
A hemorrhage, or bleeding within the skull

Isolated Hemisphere
Intracranial circulation that is fed only by the ipsilateral internal carotid artery and may be detected on prior CTA/MRA

Neurological Deterioration/Worsening
A 4 or more-point increase in NIHSS from baseline to discharge. Neurological worsening could be new or evolution/progression of the index stroke.

Permanent Cranial Nerve Palsy or Injury
Injury to cranial nerves in the vicinity of the treated carotid artery that has not resolved by three months after the intervention. Symptoms will depend on the specific nerve that is injured, such as hoarseness.

Pre-stroke disability
Obtained at baseline, but representative of the patient's status before the index stroke, assessed by mRS on medical history obtained from patient's medical chart, or family members.

Procedure Related Adverse Event
An undesirable event that occurred as a direct cause of the procedure that was not a direct cause of the study device.

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

Stroke
A neurological deficit lasting 24 hours or more attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Stroke can be subclassified as Hemorrhagic or Ischemic

Symptomatic Intracranial Hemorrhage (SICH)
New intracranial hemorrhage detected by brain imaging associated with any of the items below (Von Kummer et al. 2015):

- ≥ 4 points total NIHSS at the time of diagnosis compared to the pre-procedure NIHSS.
- ≥ 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.
- Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention.
- Absence of alternative explanation for deterioration

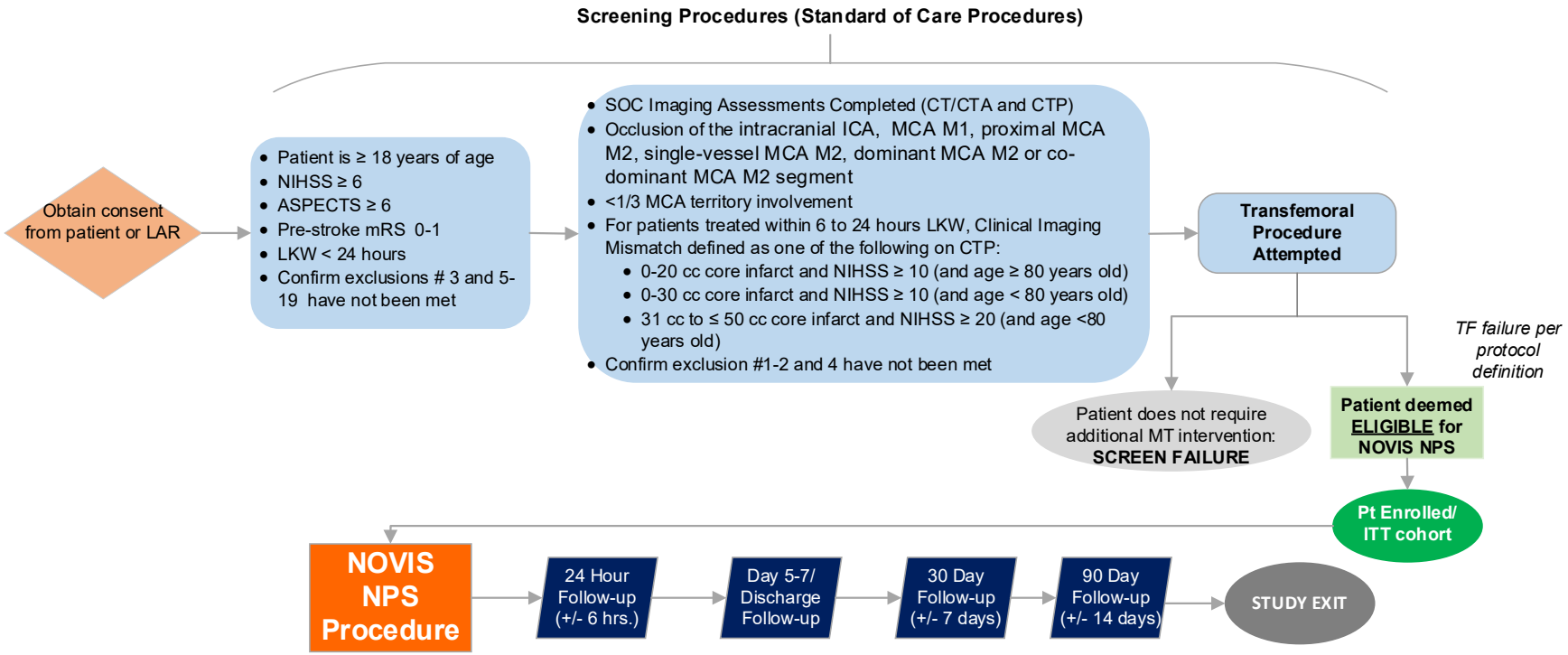
Technical Success
Successful introduction of endovascular tools through the NOVIS Transcarotid NPS.

Transient Ischemic Attack (TIA)
Temporary focal brain or retinal deficits caused by vascular disease that resolves completely in less than 24 hours.

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. The effect must have not been previously identified in nature, severity or degree of incidence in the study plan or IFU. Other unanticipated serious problems associated with the device that relates to the rights, safety or welfare of study patients may also be considered UADEs.

Vascular Access Site Complications
These complications are associated with the NITE procedure whether through the arterial or venous access and are categorized into dissections, hemorrhage, infections, perforations, pseudoaneurysms and ruptures.

Appendix 5. Patient Flow Diagram



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