The ENROUTE Transcarotid Neuroprotection System (ENROUTE Transcarotid NPS)
DW-MRI Evaluation

Clinical Protocol	SRM–2018-01
Version	0.9
Version Date	August 8, 2018

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PROTOCOL SIGNATURE PAGE

This is a prospective, single-arm, multi-center evaluation of patients requiring carotid revascularization who are treated with the FDA-cleared ENROUTE® Transcarotid Neuroprotection System (ENROUTE® Transcarotid NPS) in conjunction with the FDA-approved ENROUTE Transcarotid Stent System.

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I have read this protocol and agree to adhere to the requirements. The protocol, other documents and all necessary information will be made available to the participating sites and their personnel. As required, will discuss this material with them and ensure they are fully informed regarding protocol. The evaluation will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements as required.

Site Name	Site Location (City, State)
Physician Printed Name	
Physician Signature	Date

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1 Protocol Summary

Title	The ENROUTE Transcarotid Neuroprotection System (ENROUTE Transcarotid NPS) DW-MRI Evaluation.
Objective	To correlate pre and post procedure DW-MRI for patients treated with the transcarotid artery revascularization (TCAR) procedure.
Design	This is a prospective, single-arm, multi-center evaluation of patients requiring carotid revascularization who are treated with the FDA-cleared ENROUTE Transcarotid NPS in conjunction with the FDA-approved ENROUTE Transcarotid Stent.
Enrollment	A minimum of 50 patients and a maximum of 75.
Locations	Up to 10 sites in the United States of America and up to 2 sites in the European Union.
Primary Endpoint	Incidence of ipsilateral new white lesions by DW-MRI post procedure.
Secondary Endpoints	The following secondary endpoints will be assessed 0 to 30 days: ▪ All Stroke ▪ Neurological Death ▪ Stroke/Death in patients eligible for ROADSTER 2 • Volume of DW-MRI lesions • Location of DW-MRI Lesions • Stroke/Death in patients ineligible for ROADSTER 2 • Rate of contralateral new white lesions by DW-MRI
Patient Population	Symptomatic or Asymptomatic patients with atherosclerotic extracranial internal carotid stenosis (ICA) with or without involvement of the contiguous common artery (CCA).
Planned Schedule	First patient enrolled: November 2018 Last patient enrolled: November 2019 Last 30-day follow-up visit: December 2019

2 Principal Contacts

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3 Introduction

Cerebral embolization during carotid artery stenting (CAS) can often precipitate severe adverse neurological effects. Most major clinical studies of CAS have used distal filters (from a transfemoral route) for cerebral protection and have compared the neurologic complication rates with those of carotid endarterectomy (CEA). The contemporary absolute stroke/death rates for CEA and filter-protected CAS within a tightly proscribed randomized trial are low (2.3% versus 4.4%) (CREST). To power a trial to compare the impact of procedural and/or technical modifications (such as improved embolic protection strategies) would require several thousand patients at the minimum. New white lesions on DW-MRI of the brain occur at a much higher rate than stroke and death. Many of these lesions remain clinically covert but the impact on cognition in the long term is unknown. The ICSS sub-study revealed a 50% new white lesion rate following transfemoral CAS (which rose to 73% for filter-protected transfemoral CAS) compared with 17% for CEA. Although the incidence of new DW-MRI lesions is far higher than the incidence of clinically apparent neurological deficits. In the ICSS MRI subset, the DW-MRI lesions with the largest volume were significantly associated with the occurrence of neurologic events. Although the fate and clinical relevance of these lesions remain

unknown, their incidence makes them an attractive surrogate to maintain adequate power whilst reducing the size of the study population.

4 Device Overview and Usage

The ENROUTE Transcarotid Neuroprotection System (NPS) was 510(k) cleared by the FDA on February 9, 2015, and the ENROUTE Transcarotid Stent System was PMA Approved by FDA on May 18, 2015. Both devices are commercially available in the United States. The ENROUTE Transcarotid Neuroprotection System was granted the CE marking of conformity on January 27, 2016. The ENROUTE Transcarotid Stent System was granted the CE marking of conformity on July 2, 2013.

4.1 Device Description

The ENROUTE Transcarotid Stent System

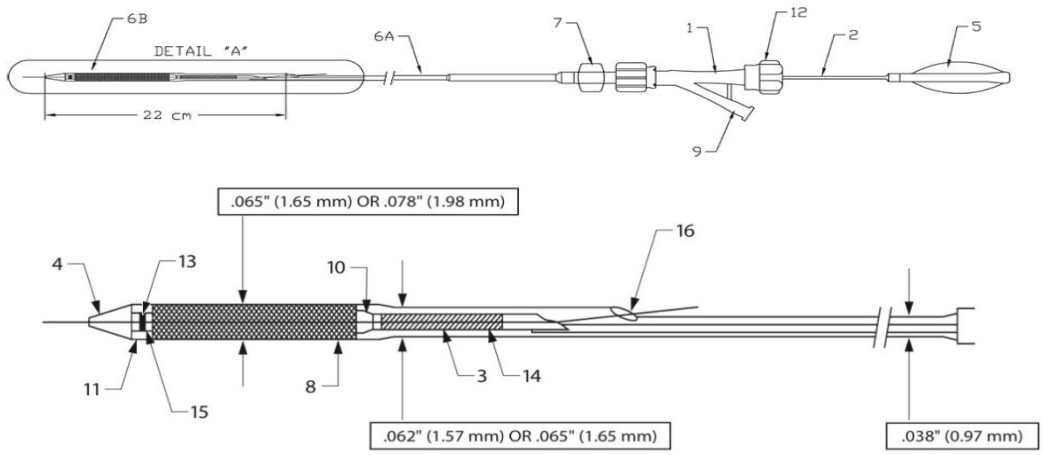
The Silk Road ENROUTE Transcarotid Stent System consists of a nitinol self-expanding stent preloaded on a 5F (.065" / 1.65 mm) or 6F (.078" / 1.98 mm) sheathed delivery system. The rapid exchange delivery system consists mainly of an inner shaft and an outer sheath with radiopaque markers, and a Tuohy Borst valve. The inner shaft consists of a support member and wire lumen. The proximal portion of the support member is comprised of a hub connected to a stainless steel wire and hypotube and distally of a stainless steel coil. The wire lumen originates distally in a catheter tip and terminates proximally at a guidewire exit port designed to accept a .014" (0.36 mm) guidewire. The outer sheath has a proximal shaft and distal outer sheath with a nominal working length of 57 cm. The self-expanding ENROUTE Transcarotid Stent System is constrained within the space between the inner shaft and the distal outer sheath, located between distal and proximal stent markers on the inner shaft. The stent expands to its unconstrained diameter when released from the deployment catheter into the carotid artery. Upon deployment, the stent forms a lattice to cover the diseased arterial segment and to push outward on the luminal surface, helping to maintain the patency of the artery. Due to the self-expanding behavior of nitinol, the stents are indicated for placement into vessels that are 1-2 mm smaller in diameter than the unconstrained diameter of the stent. Device depictions and components are provided in Figure 1. The ENROUTE Transcarotid Stent (nitinol implant) is available in 18 sizes mounted on delivery systems in two (2) crossing profiles depending on stent diameter (unconstrained). Refer to Table 1.

Non-clinical testing has demonstrated that the ENROUTE Transcarotid Stent is MR Conditional. A patient with this device can be scanned safely in an MR system meeting the following conditions:

- Static magnetic field of 1.5-Tesla or 3-Tesla, only
- Maximum spatial gradient magnetic field of 4,000 Gauss/cm (40 Tesla/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2-W/kg (Normal Operating Mode).

Under the scan conditions defined above, the ENROUTE Transcarotid Stent is expected to produce a maximum temperature rise of 2.4°C after 15 minutes of continuous scanning. In non-clinical testing, the image artifact caused by the device extends approximately 5 mm from the ENROUTE Transcarotid Stent when imaged with a gradient echo pulse sequence and a 3-Tesla MRI system. The artifact does obscure the device lumen.

Figure 1. ENROUTE Transcarotid Stent System



1. Tuohy Borst valve
2. Hypotube
3. Coil
4. Catheter Inner Shaft Tip
5. Inner Shaft Hub
6A. Proximal Shaft
6B. Distal Outer Sheath
7. Outer Sheath Luer Hub
8. Pod Housing Crimped Stent
9. Tuohy Borst Y-Connection
10. Proximal Inner Shaft Marker (Stop)
11. Outer Sheath Radiopaque Marker
12. Proximal Valve End
13. Distal Inner Shaft Stent Marker
14. Coil Sleeve
15. Wire Lumen
16. Guidewire Exit Port

Table 1. ENROUTE Transcarotid Stent and Delivery System Dimensions

ENROUTE CODES	UNCONSTRAINED STENT DIMENSIONS Diameter x Length (mm)	CROSSING PROFILE
SR-0520-CS	5 x 20	5F (.078", 1.98mm)
SR-0530-CS	5 x 30	5F (.078", 1.98mm)
SR-0540-CS	5 x 40	5F (.078", 1.98mm)
SR-0620-CS	6 x 20	5F (.078", 1.98mm)
SR-0630-CS	6 x 30	5F (.078", 1.98mm)
SR-0640-CS	6 x 40	5F (.078", 1.98mm)
SR-0720-CS	7 x 20	5F (.078", 1.98mm)
SR-0730-CS	7 x 30	5F (.078", 1.98mm)
SR-0740-CS	7 x 40	5F (.078", 1.98mm)
SR-0820-CS	8 x 20	5F (.078", 1.98mm)
SR-0830-CS	8 x 30	5F (.078", 1.98mm)
SR-0840-CS	8 x 40	5F (.078", 1.98mm)
SR-0920-CS	9 x 20	6F (.087", 2.21mm)
SR-0930-CS	9 x 30	6F (.087", 2.21mm)
SR-0940-CS	9 x 40	6F (.087", 2.21mm)
SR-1020-CS	10 x 20	6F (.087", 2.21mm)
SR-1030-CS	10 x 30	6F (.087", 2.21mm)
SR-1040-CS	10 x 40	6F (.087", 2.21mm)

The ENROUTE Transcarotid Neuroprotection System (NPS)

The ENROUTE Transcarotid Neuroprotection System (NPS) consists of three primary components: the Transcarotid Arterial Sheath, the Flow Controller, and the Venous Return Sheath. When assembled, the ENROUTE Transcarotid NPS creates an arteriovenous shunt that reverses the flow of blood at the treatment site of the carotid arteries from antegrade to retrograde due to the pressure gradient between arterial and venous pressure thereby shunting embolic particles away from the cerebral circulation. The rate of reverse flow (low or high) through the arteriovenous shunt is regulated by the Flow Controller. Subsequent iterations of the ENROUTE Transcarotid Neuroprotection System (NPS) may be used during this study.

4.2 Intended Use

4.2.1 ENROUTE Transcarotid Stent

The ENROUTE Transcarotid Stent System used in conjunction with the ENROUTE Transcarotid Neuroprotection System is indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy, who require carotid revascularization and meet the criteria outlined below.

- Patients with neurological symptoms and ≥ 50% stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and ≥ 80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
- Patients must have a vessel diameter of 4-9 mm at the target lesion, AND
- Carotid bifurcation is located at minimum 5 cm above the clavicle to allow for placement of the ENROUTE Transcarotid Neuroprotection System.

4.2.2 ENROUTE Transcarotid Neuroprotection System

The ENROUTE® Transcarotid Neuroprotection System is intended to provide transcarotid vascular access, introduction of diagnostic agents and therapeutic devices, and embolic protection during carotid artery angioplasty and stenting procedures for patients diagnosed with carotid artery stenosis and who have the appropriate anatomy described below:

- Adequate femoral venous access
- Patients must have a vessel diameter of 6 mm of the common carotid artery and is free of significant disease at the access point, AND
- Carotid bifurcation is located at minimum 5 cm above the clavicle to allow for placement of the ENROUTE Transcarotid Neuroprotection System.

5 Objective

The goal of this evaluation is to document the incidence of post procedure DW-MRI lesions (relative to baseline) in patients treated with the transcarotid artery revascularization (TCAR) procedure.

6 Design

This is a prospective, single-arm, multi-center evaluation of patients requiring carotid revascularization who are treated with the FDA-cleared ENROUTE Transcarotid NPS in conjunction

with the FDA-approved ENROUTE Transcarotid Stent System. Both the ENROUTE Transcarotid NPS and ENROUTE Transcarotid Stent System have received CE mark and are commercially available in the European Union.

7 Endpoints

7.1 Primary Endpoint

Incidence of ipsilateral new white lesions by DW-MRI 30 days post procedure.

7.2 Secondary Endpoints

The following secondary endpoints will be assessed 0 to 30 days:

- All Stroke
- Neurological Death
- Volume of DW-MRI lesions
- Location of DW-MRI Lesions
- Stroke/Neurological Death in patients eligible for ROADSTER 2
- Stroke/Neurological Death in patients ineligible for ROADSTER 2
- Rate of contralateral new white lesions by DW-MRI

8 Population

Patients participating in this evaluation will be comprised of male and female symptomatic or asymptomatic patients requiring carotid revascularization.

8.1 Patient Eligibility

Patients must meet ALL of 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 or treated using the study devices.

Note: Patients treated with TCAR within the ROADSTER 2 Post Approval Study are eligible to participate in this evaluation since this evaluation only adds non-invasive imaging before and after a routine TCAR procedure. ROADSTER 2 only excludes patients who are participating in ***investigational*** device or drug studies and does not preclude the enrollment of patients subjected to other routine medical care.

8.2 Inclusion Criteria

1. Patient must meet **one** of the following criteria regarding neurological symptom status and degree of stenosis:

   Symptomatic: Stenosis must be ≥50% as determined by ultrasound or angiogram[1] and the patient has a history of stroke (minor or non-disabling; NIHSS ≤4 or mRS ≤2), TIA and/or amaurosis fugax within 180 days of the procedure ipsilateral to the carotid artery to be stented.

   OR

   Asymptomatic: Stenosis must be ≥80% as determined by ultrasound or angiogram without any neurological symptoms within the prior 180 days.

[1] For this protocol, this is limited to CT angiogram.

2. Target vessel must meet diameter requirements for stent (refer to stent IFU for diameter requirements).
3. Patient has a discrete lesion located in the internal carotid artery (ICA) with or without involvement of the contiguous common carotid artery (CCA).
4. Patient is willing to comply with the protocol requirements and return to the treatment center for all required clinical evaluations.
5. Patient must have a life expectancy ≥ 3 years at the time of the index procedure without contingencies related to other medical, surgical or endovascular intervention.
6. Patient meets at least one of the surgical high-risk criteria listed in CMS National Coverage Determination (NCD) for Percutaneous Transluminal Angioplasty (20.7)

8.3 Exclusion Criteria

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

1. Patient has an alternative source of cerebral embolus, including but not limited to:
    a. Patient has chronic atrial fibrillation.
    b. Patient has had any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation.
    c. Knowledge of cardiac sources of emboli. e.g. left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma).
    d. Recently (<60 days) implanted heart valve (either surgically or endovascularly), which is a known source of emboli as confirmed on echocardiogram.
    e. Abnormal angiographic findings: ipsilateral intracranial or extracranial arterial stenosis (as determined by angiography or CTA/MRA ≤ 6 months prior to index procedure) greater in severity than the lesion to be treated, cerebral aneurysm > 5 mm, AVM (arteriovenous malformation) of the cerebral vasculature, or other abnormal angiographic findings.
2. Patient has a history of spontaneous intracranial hemorrhage within the past 12 months, or has had a recent (<7 days) stroke of sufficient size (on CT or MRI) to place him or her at risk of hemorrhagic conversion during the procedure (less than one-third middle cerebral artery volume).
3. Patient had hemorrhagic transformation of an ischemic stroke within the past 60 days.
4. Patient with a history of major stroke attributable to either carotid artery (CVA or retinal embolus) with major neurological deficit (NIHSS ≥ 5 OR mRS ≥ 3) likely to confound study endpoints within 1 month of index procedure.
5. Patient has an evolving stroke.
6. Patient has an intracranial tumor.

7. Patient has neurologic illnesses within the past two years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from TIA or stroke, including but not limited to: moderate to severe dementia, partial or secondarily generalized seizures, complicated or classic migraine, tumor or other space-occupying brain lesions, subdural hematoma, cerebral contusion or other post-traumatic lesions, intracranial infection, demyelinating disease, or intracranial hemorrhage).
8. Patient has had a TIA or amaurosis fugax within 48 hrs prior to the procedure.
9. Patient has an isolated hemisphere defined as the ipsilateral middle cerebral artery being supplied only by the ipsilateral internal carotid artery.
10. Patient has active bleeding diathesis or coagulopathy or will refuse blood transfusion.
11. Patient had or will have CABG, endovascular stent procedure, valve intervention or vascular surgery within 30 days before or after the intervention.
12. Myocardial Infarction within 72 hours prior to the intervention.
13. Occlusion of the ipsilateral common or internal carotid artery.
14. An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) whether or not it is associated with an ulcerated target lesion.
15. Patients with carotid string sign (a very high-grade carotid stenosis to the skull base with a long, thin, barely visible string of contrast within the true lumen of the artery.).
16. Ostium of Common Carotid Artery (CCA) requires revascularization (>50% stenosis).
17. Patient has an open stoma in the neck.
18. Patients with hostile necks due to prior neck irradiation
19. Female patients who are pregnant
20. Patient has history of intolerance or allergic reaction to any of the study medications or stent materials (refer to stent IFU), including aspirin (ASA), ticlopidine, clopidogrel, prasugrel, statin or contrast media (that can't be pre medicated). Patients must be able to tolerate statins and a combination of ASA and ticlopidine, ASA and clopidogrel or ASA and prasugrel.
21. Patient has a life expectancy <3 years with contingencies related to other medical, surgical, or interventional procedures as per the Wallaert Score and patients with primary, recurrent or metastatic malignancy who do not have independent assessment of life expectancy performed by the treating oncologist or an appropriate specialist other than the physician performing TCAR.
22. Patient has had a recent GI bleed that would interfere with antiplatelet therapy.
23. Patient is actively participating in an investigational drug or device trial (IND or IDE) that has not completed the required protocol follow-up period.
24. Patient has inability to understand and cooperate with study procedures.
25. Presence of extensive or diffuse atherosclerotic disease involving the proximal common carotid artery that would preclude the safe introduction of the study device.
26. Patient is otherwise unsuitable for intervention in the opinion of the physician.
27. Patients who cannot have MRI due to metallic implants (e.g. orthopedic implants, pacemakers, etc.)

8.4 Enrollment Determination

Patients meeting all of the inclusion criteria and none of the exclusion criteria, can be considered for inclusion in the study.

9 Patient Enrollment

A minimum of 50 patients and a maximum of 75 patients.

The first 2 cases performed at each participating site will be evaluated to ensure compliance with the procedural guidelines and to determine the suitability of the imaging for review by the core lab. If it is determined that additional training on the procedural guidelines or revisions to the imaging parameters are required, then these patients will be excluded from the primary endpoint analysis.

9.1 Enrollment Phase

Patients are considered to be enrolled after signing the informed consent and having undergone a successful TCAR procedure (e.g. the procedure was not aborted due to technical issues or due to local complications the preclude stent implantation). Patients who are screened but do not meet all study criteria are considered screen failures and may not be enrolled.

9.2 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.

Examples:

First Patient Enrolled at site #801: 801-001

9.3 Patient Discontinuation

If possible, every patient should remain in the study until completion of the required follow-up period; however, 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 Study Exit form must be completed. Factors leading to patient discontinuation may include, but are not limited to the following:

- **Patient Withdrawal**: Patient participation is voluntarily 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.
- **Physician Termination**: The physician may terminate the patient's participation without regard to the patient's consent if the Physician believes it is medically necessary.
- **Lost to Follow-up**: A patient will be considered lost to follow-up only after three unsuccessful, documented attempts to contact the patient have been made.

10 Procedures

10.1 Informed Consent

Prior to patient participation in this evaluation, the Physician must obtain written Institutional Review Board approval for the protocol and the informed consent form. The approved consent form should clearly reflect the IRB/EC approval date and protocol version.

Once the patient's eligibility has been determined, the Physician or person designated by the Physician who has been trained to the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, answer questions for the patient and ask the patient to participate in the study. The study will be explained to the study patient in lay terms and native language. If the patient agrees to participate, the informed consent must be signed and personally dated by the patient and the person completing the consent process. A copy of the signed and dated informed consent will be provided to the study patient. Study patients will be assured that they may withdraw from the study at any time and for any reason.

Failure to obtain a signed informed consent form prior to the 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).

10.2 Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) Evaluation

A DW-MRI evaluation is to be done pre, post and 30 days post the index procedure. The following sequences should be used for each evaluation.

Magnetic resonance using a 3 Tesla MR imaging scanner. Sequences : T1, T2, T2*, GRE, FLAIR, DWI and ADC map. Slice thickness: 4mm

Table 1. DW-MRI visit windows

Visit Window	Imaging Timing
Pre-procedure	≤ 72 hours prior to procedure
Post-procedure	Within 12 – 60 hours post procedure
30 days Post-procedure	30 days*(-7/+15 days)* post procedure

10.3 Pre-Procedure

Dual antiplatelet therapy and statin medications taken during the course of the study should be documented on the CRFs and a dosage indicated if possible.

Table 2. Pre-procedure Testing and Evaluations

Test / Evaluation	Timeframe Prior to Procedure *(within # days)*				
	180 days	60 days	30 days	7 days	≤ 72 hours
General Examination					
Medical History			√		
Neurological Examination[1]					
NIH Stroke Scale Modified Rankin Scale				√	
Imaging					
Bilateral Duplex Ultrasound (% of stenosis)		√			
DW-MRI					√
CTA of the head and neck	√				

[1]Every attempt should be made to have the same person conduct the exam at each visit.

10.3.1 Pre-Procedure Medication Regimen

All medications should be administered per the following medication guidelines. All medications administered should be recorded on the patient's medical record and on the CRF throughout the duration of the trial. Prior to the procedure, all patients should receive the following medications:

Table 3. Pre-Procedure Medication Regimen

Medication	Dose	Time prior to procedure	Notes
Aspirin	75-325 mg*	At least 72 hrs	A 650 mg loading dose of aspirin, provided that it is not enteric coated or extended release, at least 4 hours prior to procedure is acceptable if 325 mg dosing was not administered prior to procedure or per the Institution's standard of care.
Clopidogrel	75 mg*	At least 72 hrs	A 450 mg clopidogrel loading dose at least 4 hours prior to procedure is acceptable if 75 mg dosing was not administered prior to procedure. The physician may substitute Prasugrel, ticlopidine, ticagrelor or a generic version of Clopidogrel per the manufacturer's published guidelines. If ticlopidine or ticagrelor is prescribed, it must be administered with the appropriate safety monitoring at two weeks and at one month.

Medication	Dose	Time prior to procedure	Notes
Statin	Therapeutic dose	Daily for at least 7 days	If possible, patients who are not currently on a statin should be started on a therapeutic dose for 7 days pre-procedure if not, use loading dose. A loading dose at least 12 hours before procedure is acceptable if the patient is not already on a statin.

*As stated in the "2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary." and "ESVS Guidelines. Invasive Treatment for Carotid Stenosis: Indications, Techniques."

10.3.2 Pre-Procedure Contrast Preparation

Contrast should be drawn in to a manifold contrast injection system and allowed to rest undisturbed for a minimum of 20 minutes prior to planned usage.

At the discretion of the physician a syringe may be used for contrast injection. At least 20 minutes prior to use contrast should be drawn up into a least five 10ml luer lock syringes. Allow syringes to rest undisturbed for a minimum of 20 minutes prior to planned usage. Use of an automated contrast injector is recommended but not required.

10.4 TransCarotid Revascularization

10.4.1 Index Procedure

Responsibility for performing the index procedure may not be delegated to a Physician who has not been approved by the sponsor.

10.4.2 Procedural Medications

Heparin should be administered to achieve the desired activated clotting time (ACT). A sufficient dose should be given to achieve a target activated clotting time (ACT) of $\geq$ 250 seconds and maintained throughout the procedure.

At the discretion of the physician, procedural anticoagulation may be achieved with Angiomax (bivalirudin) which must be administered accordingly during the procedure.

The use of local or general anesthetic during the procedure is at the discretion of the physician.

IMPORTANT: Pre-treatment with a thrombolytic agent or GP IIb/IIIa blocker is NOT allowed.

10.4.3 Stenting TCAR Procedure

The ENROUTE Transcarotid Neuroprotection System (ENROUTE Transcarotid NPS) will be used for all index procedures in conjunction with the ENROUTE Transcarotid Stent System. Please refer to the IFU supplied with the ENROUTE Transcarotid NPS and Stent System for device preparation and placement.

Standard surgical means should be used to occlude the CCA during the index procedure.

After the ENROUTE Transcarotid NPS has been positioned, pre-dilatation of the lesion may be done prior to stent placement. Use an appropriately sized balloon to achieve a lumen diameter large

enough for passage of the stent delivery system. The appropriate size stent shall be selected after review of the patient's pre-procedure angiogram for determination of the reference vessel.

The choice of stent length should ensure complete coverage of the lesion. Only one stent should be used unless there is incomplete coverage of the target lesion or in the case of complications. For complications, an additional commercially available stent may be used.

IMPORTANT: Debulking devices, such as directional or rotational atherectomy and/or transluminal extraction coronary (TEC) devices may NOT be used.

10.5 Criteria for Bailout

Bailout measures are at the discretion of the physician. Emergent endovascular therapy (neurovascular rescue) may be employed as necessary to provide the best medical care for the patient.

10.6 Mechanical Failures, Malfunctions or Device Defects

All mechanical failures, malfunctions or defects involving any device component must be reported to the Sponsor in accordance with the FDA device reporting guidelines and EU Vigilance Reporting requirements.

10.7 Post-Index Procedure Medications

All medications should be administered per the following medication guidelines. All medications administered should be recorded on the patient's medical record and on the CRF throughout the duration of the trial. After the procedure, all patients (lead-in and pivotal) should receive the following medications:

Table 4.Post Procedure Medication Regimen

Medication	Dose	Duration post-procedure
Aspirin	75 – 325 mg	Daily, continued indefinitely
Clopidogrel	75 mg	Daily, for minimum of 4 weeks
Statin	Therapeutic dose	Daily, for minimum of 4 weeks

11 Post Procedure Evaluation

The following tests or procedures must be obtained as per schedule. These tests must be performed whether or not they are considered part of the Physician's standard of care.

Table 5. Post-Procedure Testing and Evaluations

Test / Evaluation	Timeframe Post-Procedure		
	Within 12 – 60 hrs post procedure	Within 24 hrs	Prior to Discharge
Neurological Examination[1]			
NIH Stroke Scale Modified Rankin Scale		√	
Imaging			
DW-MRI	√		

[1]Every attempt should be made to have the same person conduct the exam at each visit.

Prior to hospital discharge the study coordinator and/or Principal Physician at the site should ensure that the patient understands and complies with the required follow-up schedule. If possible, patients or family members may be given a calendar of required follow-up visits and telephoned by a member of the research team for a visit reminder, just prior to the follow-up date.

11.1 Follow-up

Study patient clinic evaluations must occur at multiple time-points post-procedure. The following tests or evaluations must be obtained:

Table 6. 30-day Testing and Evaluations

Test / Evaluation	30-days *(-7/+15 days)*
Neurological Examination[1]	
NIH Stroke Scale Modified Rankin Scale	√
Imaging	
Duplex Ultrasound (Bilateral)	√
DW-MRI	√

[1] Every attempt should be made to have the same person conduct the exam at each visit.

12 Assessment of Safety and Performance

Performance and safety will be monitored continuously throughout the conduct of the study.

12.1 Clinical Follow-up Visits

Patients will be contacted for clinical follow-up office visit between 30 and 45 days post procedure.

Appendix 1. Schedule of Events outlines the evaluations that are be done at each time point.

12.2 Additional Follow-up Visits

Additional patient visits may occur as clinically warranted.

13 Adverse Events

Adverse event (AE) data will be collected throughout the study and will be recorded on the Adverse Event CRF. For the purposes of this evaluation, adverse events include any stroke or neurological death.

14 Statistical Methods

No formal hypothesis testing is planned; parameter estimates will be defined using descriptive and inferential statistics.

14.1 General Considerations

Inferential statistical tests will be identified as being either one- or two-sided, and the construct of the confidence limits will be defined (e.g. 90% or 95%). Exact confidence intervals will be used for all presentations.

14.2 Endpoint Analyses and Hypothesis Testing

The objective of this registry is to provide contemporaneous estimates ascribed to the event rates (rate of new white lesions on DW-MRI) under commercial use conditions. No formal statistical hypotheses regarding safety or efficacy will be made. Additional summaries and tabulations may be presented by demographic and disease-related parameters.

15 Data Collection

15.1 Required Data

All required data for this evaluation will be collected on standardized Case Report Forms (CRFs). For the duration of the evaluation, the Physician will maintain complete and accurate documentation, including but not limited to, medical records, evaluation progress notes, laboratory reports, CRFs, device accountability logs, correspondence with the reviewing IRB/EC, sponsor and Monitor, adverse event reports, and information regarding patient discontinuation or completion of the evaluation.

The physician/institution will permit direct access to source data and documents in order for evaluation-related monitoring, audits, IRB/EC reviews, event adjudication and regulatory inspections to be performed. The physician should obtain, as part of the Data Release Consent process, permission for authorized sponsor employees, monitors or regulatory authorities to review, in confidence, and records that identify patients in this trial.

15.2 Source Documentation

Regulations require that the Physician maintain information in the patient's medical records, which corroborate data collected for the evaluation. 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 evaluation of a sufficient nature to verify the protocol eligibility criteria.
- Dated and signed notes on the date of entry into the evaluation documenting the following:

- The general health of the patient,
- 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, ECGs, lab results, CT/MRI reports.
- Notes regarding protocol-required and prescription medications taken during the evaluation (including start and stop dates if known).
- Patient's general health and medical condition upon completion of or withdrawal from the evaluation.

15.3 Case Report Forms

Data will be accurately recorded on the Case Report Forms (CRFs) in an electronic data capture system by site personnel that have been trained on the protocol and CRF completion.

15.4 Record Retention

All clinical sites will maintain all records pertaining to this evaluation for a minimum of two years (or as long as required by specific institutional guidelines) after the evaluation is discontinued. The sponsor will notify the clinical sites of the discontinuation or planned end of evaluation as well as where applicable, the Physician and/or Silk Road Medical will inform the IRB or EC/Competent Authorities

15.5 Confidentiality

All data and information collected during this evaluation will be considered confidential by the Sponsor. All data used in the analysis and summary of this evaluation will be anonymous, and without reference to specific patient names. Access to patient files will be limited to authorized personnel of the Sponsor, the Physician, Clinical site research staff and authorized Regulatory Authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this evaluation.

16 Sponsor Responsibilities

As the Sponsor, Silk Road Medical, has the overall responsibility for the conduct of the evaluation including assurance that the evaluation satisfies the regulatory requirements of the appropriate regulatory agencies.

16.1 Training of Physicians and Site Personnel

Physicians and site personnel will be trained on the following aspects of the evaluation:

- Protocol
- Case Report Forms
- Reporting Responsibilities
- Device Instructions for Use
- Confidentiality

17 Monitoring

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

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

18 Site Responsibilities

18.1 Site Personnel Responsibilities

18.1.1 Principal Physician

- Ensures that the appropriate IRB or EC approvals are obtained as required,
- is responsible for the overall conduct of the evaluation at the site,
- is trained in the use of the devices,
- is trained on the evaluation protocol, forms, and procedures.

18.2 Physician Responsibilities

The Physician is responsible for ensuring that this evaluation is conducted according to this Clinical Protocol, and all conditions of IRB/EC approval and applicable regulations. The Physician is responsible for ensuring that Data Release Consent is obtained, if required. The data release form may be translated into the applicable language.

Patients must be informed that their medical records may be subject to review by SRM (Sponsor), its authorized designee, or local regulatory representatives. Patients will be informed that they are free to refuse to participate in this evaluation without loss of benefits to which they are otherwise entitled, and that if they choose to participate, they may withdraw at any time without prejudice to future care.

18.2.1 Physician Records

The Physician will maintain complete, accurate and current evaluation records. Records shall be maintained during the evaluation and for two years (or as long as required by specific institutional guidelines) after the date on which the evaluation is terminated or completed, or the date the records are no longer required.

18.2.2 Patient Records

Patient records include copies of all completed Case Report Forms and supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.).

At any time, patients are entitled to ask the Physician for access to all the information collected in this study relating to him or her. If any of the information is inaccurate, the subject is entitled to request to the physician that the appropriate changes or corrections are made.

18.2.3 IRB/EC Information

The physician is responsible for maintaining any information pertaining to the IRB/EC review and approval as required by local law.

18.2.4 Other

The physician is responsible for any other records that may be required by applicable laws.

19 Core and Central Laboratories

19.1 DW-MRI Core Laboratory

All DW-MRI evaluations will be sent to the DW-MRI core laboratory for review. The evaluation will be reviewed using a standard method per the core laboratory guidelines and these data will be used for final analysis.

20 Protocol Deviations

A protocol deviation is defined as an event where the physician or site personnel deviate from the protocol or procedures.

In the event that a physician does not comply with the Physician agreement, and/or the protocol, the physician will be notified of their non-compliance, and the circumstances will be reviewed by the sponsor.

21 Device Accountability

Product used in this evaluation are FDA approved/cleared and have CE marking. The devices are commercially available and device accountability is not required.

22 Ethics

This evaluation is a non-interventional post market evaluation, which means that IRB/EC approval depends on local law / hospital requirements. If not required, written documentation from the physician should be maintained with the records

22.1 Protocol Amendments

Approved protocol amendments will be provided to the Physicians by the sponsor prior to implementing the amendment. The Physician will be responsible for notifying or obtaining approval from the reviewing IRB/EC of the protocol amendment, if required by local law/hospital. The IRB/EC acknowledgement/ approval of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must also be provided to the Sponsor.

22.2 Data Release Consent

If required, by local law / hospital the physician should obtain written Data Release Consent prior to releasing personal information of the patient. An IRB/EC approved Data Release Consent may be required according to local law/hospital requirements.

22.2.1 Data Release Consenting Procedures

During the Data Release Consent discussion, the physician or his/her designee must fully inform the subject of the evaluation in a non-technical wording understandable for the patient. The patient must have ample time and opportunity to inquire about details of the evaluation, and to decide whether or not to participate. All questions about the evaluation should be answered to the satisfaction of the patient.

After all persons have signed and dated the Data Release Consent form the physician must provide the patient with a copy of the signed and dated Data Release Consent form.

23 Use of Information and Publication

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

At the conclusion of this evaluation, 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 evaluation 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 thirty (30) days prior to any 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. 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 evaluation.

24 Termination

The Sponsor will monitor the progress of the evaluation. If warranted, the evaluation may be suspended or discontinued early if there is inadequate patient enrollment.

Appendix 1. Schedule of Events

PROCEDURE/TEST	Pre-Procedure (within # of days)					Procedure	Post-Procedure			Follow-up Visits
	180 days	60 days	30 days	7 days	≤72 hrs		Within 24 hrs	Prior to Discharge	Within 12 – 60 hours post procedure	30-days (-7/+15 days)
Informed Consent		X								
Neurological Examinations[1]										
NIH Stroke Scale Modified Rankin Scale				X			X			X
Imaging										
Bilateral Duplex Ultrasound (% of stenosis)		X								X
CTA[2]	X									
DW-MRI					X				X	X
Other Assessments										
Medical History			X							
Medications		X				X	X	X		X
Adverse events						X	X	X		X

[1] Must be performed by a Neurologist, NIHSS-certified personnel or other designee. Every attempt should be made to have the same person conduct the exam at each visit. The primary operator may not conduct the neurological exam on the treated patient.

[2] The suitability of access site and distance from the clavicle to the bifurcation (as part of standard of care) may be measured by computerized axial tomography (CT) angiography in accordance with the FDA approved labeling.

Appendix 2. Case Report Forms

Case Report Forms are on file separately at Silk Road Medical

Document #	Title
SRM-2018-08-CRF01	Pt Registration
SRM-2018-08-CRF02	Medical History
SRM-2018-08-CRF03	Procedure
SRM-2018-08-CRF04	Devices
SRM-2018-08-CRF05	Follow-up
SRM-2018-08-CRF06	Neuro Exam
SRM-2018-08-CRF08	Protocol Deviation
SRM-2018-08-CRF09	Adverse Events
SRM-2018-08-CRF07	Study Exit
SRM-2018-08-CRF010	DW-MRI

Appendix 3. Physician List

Physician list will be kept on file separately.

Appendix 4. Definitions

Access Site Complication
A localized collection of extravasated blood in subcutaneous tissue at the access site as described and stratified as Procedural in section 12.1 Post Procedure Surgical Wound Management of this protocol.

Acute Device Success
Defined as ENROUTE Transcarotid NPS was delivered (vascular access achieved), reverse flow was attempted and established, and the device retrieved / removed from vasculature. If sheath placement is attempted but unsuccessful it will be considered an acute device failure. If procedure is aborted (e.g. patient isn't cooperative, change in health status, other extenuating circumstance, etc.) before both sheaths are placed or reverse flow is attempted it is not considered a device failure. Aborted procedures will not be included in Success rate calculations.

Amaurosis Fugax
A temporary (≤24 hours) loss of vision in one eye due to insufficient blood flow to the retina.

Asymptomatic Patient
Patient does not have a history of symptoms, stroke or TIA (hemispheric or ocular), in the prior 180 days.

CABG
Coronary artery bypass graft.

Carotid String Sign

A very high-grade carotid stenosis to the skull base with a long, thin, barely visible string of contrast within the true lumen of the artery.

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

Closure
Closure is divided into two categories:

Abrupt Closure The occurrence of new severely reduced flow within the target vessel that persists, and requires rescue by a non-assigned treatment strategy, (including emergency surgery) or results in stroke or death. Abrupt closure requires a proved association with a mechanical dissection of the treatment site or instrumented vessel, thrombus or severe spasm. Abrupt closure does not connote "no reflow" (due to microvascular flow limitation), in which the carotid artery is patent but has reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application does reverse the closure.

Late Closure Defined as abrupt closure that occurs after the index procedure is completed, and the patient has left the angiography suite, and before the 30-day follow-up endpoint.

Cranial Nerve Palsy or Injury
Injury to cranial nerves in the vicinity of the treated carotid artery that has not resolved by one month and six months after the initial procedure. Symptoms will depend on the specific nerve that is injured, such as difficulty swallowing or paralysis of facial muscles.

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 undesirable event that was directly caused by the device.

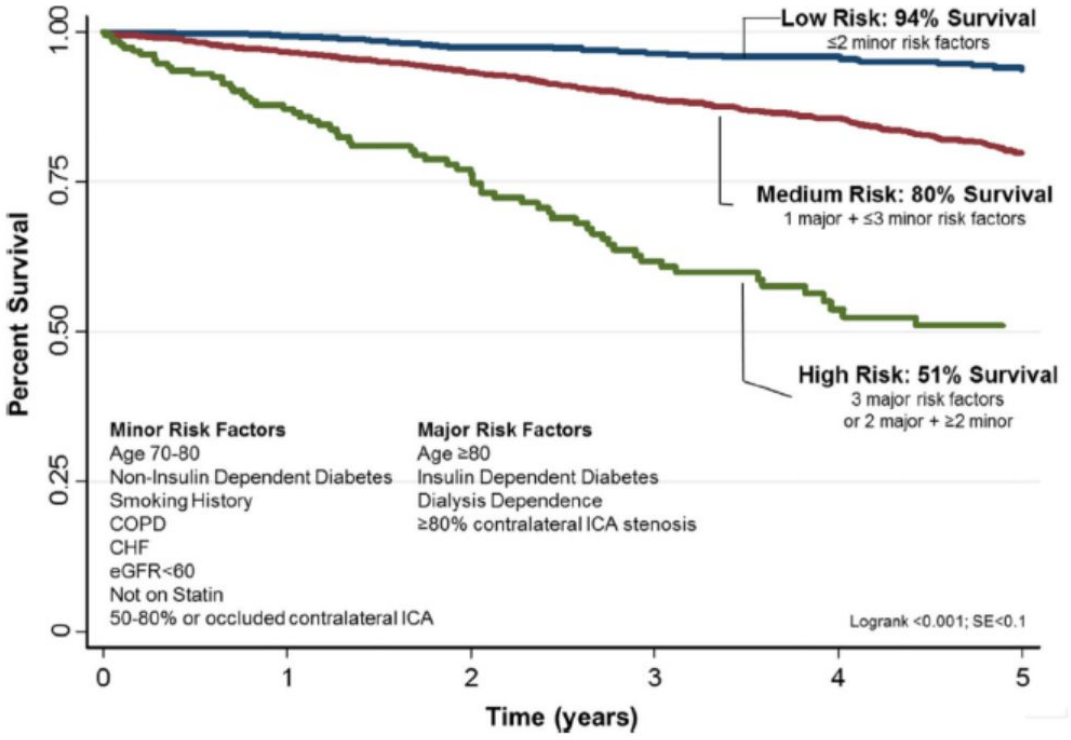
Dissection
A tear or damage to the intimal wall or lining of an artery (may or may not be flow limiting).

Emergent CEA
Carotid endarterectomy performed on an urgent or emergent basis for severe vessel dissection, treatment failure resulting in vessel occlusion or inability to access the target vessel.

Intolerance to Reverse Flow
The inability of a patient to tolerate the reversal of blood flow in the carotid artery during the index procedure. Defined as unresolved neurological deficit after antegrade flow restoration. Transient intra-procedural neurological changes, attributed to reverse flow, are not considered intolerance or an adverse event.

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

Life Expectancy
Defined as ≥ 3 years at the time of the index procedure without contingencies related to other medical, surgical or endovascular intervention. Also defined as <3 years without contingencies related to other medical, surgical, or interventional procedures as per the Wallaert Score and patients with primary, recurrent or metastatic malignancy who do not have independent assessment of life expectancy performed by the treating oncologist or an appropriate specialist other than the physician performing TCAR.



Major Adverse Event (MAE) Rate
A composite rate of death, stroke and myocardial infarction

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

Procedure Success
Technical Success without the occurrence of MAE 30-days post procedure.

Restenosis
Any narrowing of the treated segment occurring greater than 30 days after the procedure.

Serious Adverse Event (SAE)
Any adverse event that:

- led to death
- led to a serious deterioration in the health of the patient that
    - resulted in a life-threatening illness or injury
    - resulted in a permanent impairment of a body structure or a body function
    - required in-patient hospitalization or prolongation of existing hospitalization
    - resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

Stroke
A neurological deficit 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).

Major Stroke
NIH ≥5
Rankin ≥3

Note: If NIH ≥4 at enrollment, any change ≥5 is considered a major stroke. If Rankin ≥3 at enrollment, and change ≥1 is considered a major stroke

Minor Stroke
NIH ≤4
Rankin ≤2

Note: If NIH ≥4 at enrollment, any change ≤4 is considered a minor stroke

IMPORTANT: The determination of stroke and stroke severity is based upon clinical presentation only. Imaging will not be used to confirm a diagnosis of stroke.

Symptomatic Patient
Patient with history of ipsilateral TIA, amaurosis fugax or stroke (minor or non-disabling; NIHSS ≤4, **OR** mRS ≤2) within 180 days prior to the index procedure.

Technical Success:
Acute Device Success with successful introduction of interventional tools.

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

Vascular Complication
Includes dissection, psuedoaneurysm, hematoma, arteriovenous fistula, thrombus formation, embolization and any vascular complication that may be attributed to the procedure or devices used during the carotid stenting procedure AND that requires surgical repair, surgical wound revision, transfusion, etc.

Appendix 5. Procedural Guidelines

The following are procedural guidelines for contrast injection and for pre-dilatation and post-dilatation regardless of stent type:

- Contrast injection should be through an automated contrast injector with manifold system. The injector (100mls or 150mls) should be filled with contrast 20 minutes in advance of the first contrast injection in order to allow the contrast to “degass”.
- Manifold settings:
    - Flow rate: 10 ml/s
    - Volume: 5ml
    - Injection duration: 0.5
    - Pressure limit: 600 psi
    - Delay: 0
- Post dilatation balloon size:
    - Females ≤ 4.5 mm x 20 mm
    - Males ≤ 5.5 mm x 20 mm
- Inflation pressure should be according to the balloon instructions for use and the balloon should be slowly deflated.
- Flow reversal should be continued ≥ 1 minute after post dilatation.
- Aspirate through the side-arm of the NPS arterial sheath when removing it.