Medtronic ELEVATE Study - MDT19025TRACER
EvaLuate EndoVascular Treatment of Acutely Ruptured Shallow Intradural Aneurysms With the Pipeline™ Flex Embolization Device With Shield TEchnology™ (ELEVATE)
Clinical Investigation Plan Version H
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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	**E**va**L**uate **E**ndo**V**ascular treatment of **A**cutely ruptured wide-neck intradural aneurysms with the Pipeline™ Flex Embolization Device with Shield **TE**chnology™ (**ELEVATE**)
Clinical Investigation Plan/Study Identifier	MDT19025TRACER
Study Product Name	Pipeline™ Flex Embolization Device with Shield Technology™
Sponsor/Local Sponsor	Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic) 5290 California Avenue Irvine, California, 92617 United States Telephone: 949-837-3700 Fax: 949-490-3742 Local Sponsor - Canada: Medtronic of Canada ULC. 99 Hereford St. Brampton, ON L6Y 0R3 Canada Telephone: 1-800-268-5346
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2. Synopsis

Title	EvaLuate EndoVascular treatment of Acutely ruptured wide-neck intradural aneurysms with the Pipeline™ Flex Embolization Device with Shield TEchnology™ (**ELEVATE**)
Clinical Study Type	Investigational Device Exemption (IDE) Study (interventional)
Product Name	Pipeline™ Flex Embolization Device with Shield Technology™ (Pipeline™ Shield Device)
Sponsor	Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic) 5290 California Avenue Irvine, California, 92617 United States Telephone: 949-837-3700 Fax: 949-490-3742
Local Sponsor	Medtronic of Canada ULC. 99 Hereford St. Brampton, ON L6Y 0R3 Canada Telephone: 1-800-268-5346
Indication under investigation	The Pipeline™ Flex Embolization Device with Shield Technology™ is indicated for the endovascular treatment of adults (22 years of age or older) with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone.
Product Status	Pipeline™ Shield Device is an approved, commercially available device. It is not currently approved in the U.S. or Canada for the indication under investigation.
Investigation Purpose	To assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck (neck ≥4mm or dome to neck ratio ≤1.5) intradural aneurysms not amenable to surgical clipping and coiling alone.
Study Design	Multicenter, prospective, single-arm, adaptive IDE study with follow-up at 30 days, 90 days, 180 days and 365 days. • Enrollment Duration: Approximately 20 months • Follow-up: 365 days • Total Study Duration: Approximately 5 years

Primary Endpoints	Primary Safety Endpoint: Incidence of major stroke* in the territory supplied by the treated artery or neurological death through 365-day follow-up. Primary Effectiveness Endpoint: Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure. *Major stroke is defined as a stroke which is present for ≥ 24 hours and increases the NIH Stroke Scale (NIHSS) of the subject by ≥ 4.
Secondary Endpoints	1. Incidence of Pipeline™ Shield Device deployment success* 2. Incidence of target aneurysm rebleed through 180-day and 365-day follow-up post-procedure 3. Incidence of neurological hemorrhagic serious adverse events post-procedure through 180-day and through 365-day follow-up 4. Incidence of ipsilateral major stroke# or neurological death post-procedure after 30 days through 180-day and through 365-day follow-up 5. Incidence of any ipsilateral stroke post-procedure after 30 days through 180-day and through 365-day follow-up 6. Incidence of good clinical outcome (mRS 0-2) at 30-day, 180-day, and 365-day follow-up 7. Incidence of parent artery thrombosis through 365-day follow-up 8. Incidence of in-construct stenosis > 50% through 365-day follow-up 9. Incidence of target aneurysm retreatment through 180-day and through 365-day follow-up 10. Incidence of peri-/post-procedural serious adverse events related to the device, procedure or antiplatelet therapy through 180-day and through 365-day follow-up 11. Incidence of neurological death or major stroke** post-procedure through 180-day follow-up 12. Incidence of complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 180-day follow-up post-procedure *Device deployment success is the successful implantation of the device at the target location. **Major stroke: A stroke, which is present for ≥ 24 hours and increases the NIHSS of the subject by ≥ 4.

Sample Size & Study Centers	Up to 200 subjects may be enrolled (consented) to attain a target sample size of 100 evaluable subjects who will undergo treatment with available data up to 365 days. The sample size will be re-evaluated based on the interim analysis outcomes. To avoid site-specific bias, the attempted procedure will be allowed for a maximum of 20% of the total number of evaluable subjects at each participating investigational site. Up to 45 investigational sites may participate; inclusive of up to 40 investigational sites in the U.S. and up to 5 investigational sites outside U.S. (OUS).
Inclusion/ Exclusion Criteria	**Inclusion Criteria:** Subjects for this study must meet ALL of the following criteria: Imaging Criteria assessed by Physician Screening Committee: 1. Subject has a previously untreated, wide neck (neck ≥4mm or dome to neck ratio ≤1.5), intradural, side-wall target aneurysm including a blister, fusiform, saccular or dissecting aneurysm that is not amenable to surgical clipping and coiling alone, as confirmed on conventional digital subtraction angiography (DSA). 2. Subject has a target ruptured intracranial aneurysm with a proximal and distal vessel diameter suitable for treatment using available device sizes of the Pipeline™ Shield Device. Clinical Criteria: 3. Subject is ≥ 22 and ≤ 80 years of age at time of consent. 4. Subject has an acutely ruptured aneurysm (within the last 30 days prior to the planned index procedure) with Hunt and Hess Scale 1, 2 or 3. 5. Subject or subject's Legally Authorized Representative (LAR) has provided written informed consent using the IRB/EC approved Informed Consent Form and agrees to comply with Clinical Investigation Plan requirements. HIPAA/data protection authorization has been provided and signed by the subject or subject's LAR. **Exclusion Criteria:** Subjects shall be excluded from the study if ANY of the following conditions exist: Imaging Criteria assessed by Physician Screening Committee: 1. Subject's vessel characteristics (e.g. severe vasospasm, tortuosity, stenosis, morphology) precludes safe endovascular access to the aneurysm to treat with the Pipeline™ Shield Device. 2. Subject has aneurysm vessel characteristics (e.g., parent vessel stenosis, irregular morphology) that would preclude the device from fully

	conforming to the parent vessel to reduce any risk of embolic complications, retreatment, or device movement. 3. Subject has true bifurcation aneurysm or aneurysm with vessels that cannot be separated from the fundus with the placement of the Pipeline™ Shield Device. Clinical Criteria: 4. Subject with intraparenchymal hemorrhage. 5. Subject is unable to undergo Nasogastric tube/Orogastric tube placement prior to device placement. 6. Subject has a pre-morbid mRS > 2. 7. Subject requires treatment of another aneurysm with another treatment modality within the affected territory of the target aneurysm during the study period. 8. Subject has a target ruptured aneurysm that is thought to be mycotic, including those caused by left atrial myxoma, or subject has an active systemic bacterial infection. 9. Subject with a requirement for continuous anti-coagulation. 10. Subject has a malignant brain tumor or vascular malformation (e.g. arteriovenous malformation). 11. Subject's target ruptured aneurysm has not been confidently determined by the treating physician to be the source of SAH. 12. Subject with known allergy to platinum or cobalt chromium alloy (including the major elements platinum, cobalt, chromium, nickel or molybdenum). 13. Subject has a known hypersensitivity to ticagrelor or aspirin. 14. Subject is unable to undergo DSA or DSA is determined unsuitable by the treating physician. 15. Subject has a serious or life-threatening comorbidity that could confound study results. 16. Subject is at high risk of noncompliance per treating physician due to reasons including but not limited to a history of substance abuse. 17. Subject is unable to complete scheduled follow-up assessments due to comorbidities, geographical limitations, or a life expectancy of less than 24 months. 18. Female subject, of child-bearing potential, who is pregnant (confirmed with a positive pregnancy test) or breastfeeding at the time of admission or plans to become pregnant during their participation in the study.

	19. Subject is participating in another clinical trial at any time during the duration of the study that could confound the treatment or outcomes of this investigation. 20. Presumed septic embolus, or suspicion of microbial superinfection. 21. Subject with a known active COVID-19 viral infection. 22. Subject in whom a pre-existing stent is in place in the parent artery at the target aneurysm location.
Background and Rationale	Approximately, 3% of the population harbors an unruptured intracranial aneurysm[1] (UIA) and as many as 29% of UIA were reported to rupture during a lifelong follow-up[2] resulting in aneurysmal subarachnoid hemorrhage (aSAH). An estimated 30,000 people in the United States suffer an aneurysmal rupture each year.[3] Typically, aSAH is associated with a high early case fatality rate, occurs at a relatively young age compared with other types of stroke, and many survivors are left in a functionally dependent state.[4-6] Currently published literature suggests that patients with aSAH have poor outcomes with[6-8] and without treatment.[9,10] Korja et al. and Nishioka et al. reported natural history of ruptured but untreated intracranial aneurysms[9,10] and found that during a lifelong follow-up of 510 untreated aSAH patients, the 1-year mortality rate was 65%, 5-year mortality 69%, and 10-year mortality 76%.[9] Even in cases of ruptured aneurysms that were amenable to treatment such as surgical clipping and endovascular coiling, high mortality rates and poor outcomes have been reported. Case fatality rates for treated aSAH patients range between 32% and 67%,[11] with the majority of studies in a review by Nieuwkamp et al., reporting case fatality rates of more than 40%.[5] A meta-analysis of 27 studies that included 11,568 patients with ruptured intracranial aneurysms (RIAs) concluded that endovascular coiling yields a better clinical outcome in RIAs than surgical clipping.[12] However, coil embolization of RIAs may be challenging based on aneurysm size and morphology as well as characteristics of the vessel wall.[13-16] Morbidity and mortality rates ranging between 13.33% - 50%[17-20] and 6.67% - 25%,[17-20] respectively, have been reported in patients with unclippable and uncoilable RIAs after alternative treatments such as wrapping, bypass with parent artery trapping, microsurgical wrapping with autologous muscle and parent artery occlusion.[17-20] Endovascular reconstruction of the diseased segment with flow diverters has gained increasing acceptance[16,21,22] due to lower rate of recurrence[23] and procedure-related mortality[24] in cases where surgical clipping, coil embolization or stent-assisted coiling cannot be used.[25-29] Flow diverters may present a viable treatment option for RIAs that are not readily amenable to first-line treatments such as coil embolization or surgical clipping,[21] or when traditional treatment methods are unfeasible.[16,22]

Treatment of unruptured intracranial aneurysms (UIAs) with the Pipeline™ Embolization Device (PED) and Pipeline™ Flex Embolization Device (Pipeline™ Flex Device) have demonstrated high rates of long-term complete occlusion, low rates of retreatment and low rates of adverse transient and persistent neurologic events in large and giant wide-necked intracranial aneurysms.[30-34]

However, PED still has associated risks such as ischemic complications, including the risk of thromboembolism and stenosis.[35-38] These risks may be due to the high surface area of metal coverage of PED (metal coverage higher than that of self-expanding stents).[35-38] A meta-analysis that reviewed > 1700 aneurysms treated with flow diverters found that ischemic complications were reported in most of the included studies with an overall mean rate of 4.1% (range: 1% - 14.2%) and significant stenosis being reported at an overall rate of 6.8% (range: 0% - 18%).[38] Thus, to reduce ischemic and stenosis complications, it is expected that new generation flow diverters incorporate modifications to existing flow diverters.[39-41]

Thromboembolic complications (e.g. thrombosis) can result due to surface activation (vascular endothelial/vessel wall injury), disruption of blood flow, or alterations in the constitution of the blood (hypercoagulability) based on the principles of Virchow's triad.[42] The Virchow's triad is applicable irrespective of vessel bed location. Of the three contributing factors for the thromboembolic complications, surface or contact activation is influenced by device material.[42] Flow diverters which are implanted intraluminal typically have high metal coverage (30-35%) may therefore contribute to material contact activation. Continued improvement of the Pipeline™ family of devices resulted in the development of the third-iteration flow diverter, Pipeline™ Flex Device with Shield Technology™ (Pipeline™ Shield Device), to address surface activation due to device materials (material thrombogenicity).

The Shield Technology™ surface modification applied to the implant is a well-understood, inert, non-biodegradable, synthetic phosphorylcholine (PC) polymer material that is chemically bonded to the braid surface. The polymer is a chemically derived material, created to mimic the outer membrane of a human red blood cell. Shield Technology™ reduces the material thrombogenicity of the braid surface compared to the bare metal Pipeline™ Flex Device implant based on bench data with human platelets and plasma.[43-50] Recent reports[50,61,62] with the use of the Pipeline™ Shield Device (with single antiplatelet agent) for treatment of ruptured and/or fusiform/dissecting aneurysms show preliminary evidence supporting the safety and effectiveness of the Pipeline™ Shield Device in treating these complex aneurysms. Thus, the Pipeline™ Shield Device is best suited to be evaluated for the potential of

	using flow diverters in treatment of ruptured aneurysms that are not amenable to surgical clipping and coiling alone. Although there are multiple publications describing the use of flow diverters,[16,21,22] including the Pipeline™ Shield Device,[22,40,51,52] in RIAs, no structured, prospective, externally monitored and independently adjudicated study of the Pipeline™ family of devices (or any flow diverter) for the treatment of RIAs has been performed. Especially, there are no studies assessing flow diverters in aneurysms that are ruptured, wide-neck, and not amenable to surgical clipping and coiling alone. Thus, the ELEVATE study is designed as a prospective, single-arm, multicenter, adaptive IDE study to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone.
Study Procedures and Assessments	**Pre-screening:** Upon admission to treating hospital, subjects will be clinically evaluated in the same manner as any routine acute subarachnoid hemorrhage subject. Subjects will be pre-screened with an initial evaluation of the inclusion/exclusion criteria and any tests/procedures that are routinely performed as standard of care, which can be completed without obtaining informed consent. **Treatment/Follow-up:** Subjects are enrolled into the study at the point of consent. Eligible subjects will be treated with the Pipeline™ Shield Device per the investigational Instructions For Use (IFU). The study will consist of the following study visits: • Baseline screening • Procedure • 24-hour (± 12 hours) Post Procedure • Prior to discharge • 30-Day (± 14 days) Follow-up • 90-Day (± 28 days) Follow-up • 180-Day (± 28 days) Follow-up • 365-Day (± 56 days) Follow-up

	Baseline[1] Screening	Index Procedure		Post Procedure		Follow-up[12]				
		Pre-implant	Post-Implant	24-hour	Prior to discharge	30-day[15]	90-day	180-day	365-day	Un-scheduled
	-	*Day 0*	*Day 0*	*± 12 hours*	-	*± 14 days*	*± 28 days*	*± 28 days*	*± 56 days*	-
CT or MRI	◆[7]			◆	◆[11]	◆[11]	◆[11]	◆[11]	◆[11]	◆[11]
Inclusion/ Exclusion	◆									
Demographics	◆									
Medical/Surgical History	◆									
COVID-19 testing	◆[10]				◆[10]	◆[10]	◆[10]	◆[10]	◆[10]	◆[10]
Concomitant Medications	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Pregnancy Test	◆[3]									
Hunt and Hess Scale	◆									
Modified Rankin Scale (mRS)	◆[4]				◆[19,5]	◆[5]	◆[5]	◆[5]	◆[5]	◆[13]
NIH Stroke Scale (NIHSS)	◆			◆[6]		◆[6]	◆[6]	◆[6]	◆[6]	◆[13]
Clinical Vignette					◆[18]			◆[18]		
Informed Consent	◆									
CIP Specified Medication			◆	◆	◆	◆	◆	◆[17]		
Glasgow Coma Scale	◆			◆						
Digital subtraction angiography (DSA)		◆[8]	◆		◆	◆[11]	◆[11]	◆	◆	◆[11]
Adverse Event		◆[9]	◆	◆[14]	◆[14]	◆[14]	◆[14]	◆[14]	◆[14]	◆[14]
Laboratory tests[2]		◆			◆					
Fisher Grading Scale	◆									
ARU/PRU test(s)					◆[16]					

[1] Screening assessments and baseline visit may be conducted on Day 0 prior to the procedure.

[2] Laboratory tests include CBC, CHEM-7, and coagulation profile. Prior to discharge, if multiple lab values are available, the one closest to discharge must be recorded in eCRFs.

[3] Pregnancy test (serum or urine) is only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test.

[4] Premorbid modified Rankin Scale is completed any time prior to procedure by obtaining verification from an individual aware of the subject's functional status prior to SAH (e.g., family member, friend, etc.).

[5] mRS to be carried out by a certified independent assessor. mRS assessment at 90 days post-stroke must also be performed by a certified independent assessor.

[6] NIHSS to be carried out by a delegated qualified site study personnel.

[7] CT imaging is required to confirm SAH at baseline screening.

[8] Pre-procedure DSA image must be sent to the PSC for review; approval by PSC is needed in order for subject to be treated with the Pipeline™ Shield Device.

[9] Collection of adverse events will start from the point of arterial puncture. Screen Failure subjects and Procedural Screen Failure subjects will be followed for safety until subject is exited from the study. Subjects with an unsuccessful implant procedure will be followed for safety at 180-day post-procedure.

[10] If performed per SOC, collect data for COVID-19 testing.

[11] To be collected if conducted per standard of care (SOC). Any images taken per SOC should be sent to the Core Lab.

[12] Follow up schedule will be based on Time 0, which is the day of the last device implant during index hospitalization (i.e., when staged procedure is performed). If no staged procedure occurred, then Time 0 will equal Day 0.

[13] NIHSS and mRS assessments will be required only for those subjects with any presumed events of neurological nature. If mRS assessment is carried out at an unscheduled visit 90 days post-stroke, the assessment should be carried out by a certified independent assessor.

[14] For stroke events, NIHSS will be performed at the time of event, at 24 hours and at discharge; mRS must be completed a minimum of 90 days post-stroke event.

[15] If the subject is still in the hospital at the start of the 30-day visit window then the 30-day visit should be completed while the subject is in the hospital.

[16] Aspirin Reaction Units (ARU) test will be done at 24 - 48 hours post-procedure in each subject (after at least one dose of aspirin has been given and after the effects of Glycoprotein IIb/IIIa medication, eptifibatide or tirofiban, have dissipated based on the drug half-life). Subject(s) with ARU ≥ 550 units will be considered "non-responder(s)" to aspirin. For subjects who are non-responders to aspirin, P2Y12 Reaction Units (PRU) test will be performed within 24 hours of the ARU test (after at least one dose of ticagrelor). PRU levels within therapeutic range of ≥ 60 and ≤ 200 are acceptable. If subject's PRU levels are within the therapeutic range, subject will be given ticagrelor (90 mg BID) for a minimum of 6 months. If PRU levels are outside the therapeutic range, the investigator will appropriately switch the maintenance dose of antiplatelet medication to clopidogrel (Plavix) 75 mg QD or prasugrel (Effient) 10 mg QD for a minimum of 6 months after confirming the subject's responsiveness to either of these anti-platelet agents by repeated PRU tests, as needed. Note that prior to carrying out the PRU test and starting the maintenance dose, subjects should be administrated a loading dose of clopidogrel (600 mg) or prasugrel (60 mg).

[17] Subject is required to take CIP specified medication for a minimum of 180 days.

[18] If independent mRS assessor scores the mRS as ≥3, the investigator or physician involved in the management and care of the subject shall assess and document the subject's cause of disability. If applicable, the 180-day clinical vignette will be completed at the 90-day post-stroke unscheduled visit.

[19] mRS to be collected at discharge.

Antiplatelet/Anticoagulation Medication Management:

Subjects will be administered medication as described below.

Pre-Procedure	No study-specific antiplatelet or anticoagulation agents will be given prior to device placement.
Intra-Procedure	• General anesthesia medication per standard of care • Medication administered during procedure, as applicable

	Post- Implant Medication (Immediately after Pipeline™ Shield Device implant)	• Half loading dose of Glycoprotein IIb/IIIa inhibitor: o Eptifibatide (Integrilin): 90 µg per Kg **OR** o Tirofiban (Aggrastat): 12.5 µg per Kg
	Post-Procedure	• Ticagrelor (Brilinta) o 180 mg loading dose through NG tube or OG tube followed by, o 90 mg BID for 72 hours post procedure • Aspirin o 81 mg QD for 72 hours post procedure followed by, o 81 mg BID for a minimum of 6 months
	Aspirin Reaction Units (ARU) test (and $P2Y_{12}$ Reaction Units (PRU) test for aspirin non-responders) will be performed to determine each subject's suitability to an antiplatelet medication that will be administered and maintained for a minimum of 6 months.	
Safety Assessment	All adverse events (AEs) will be collected and evaluated from the point of arterial puncture through study exit for all subjects enrolled in the study. All AEs will be reported with their start date, action taken, severity (e.g., mild, moderate, or severe), causality assessment, seriousness and outcome in the subject's medical records and in the eCRF.	
Statistics	**Primary Hypothesis for Evaluating Study Success** Primary Safety Endpoint: Incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up. H_o: Incidence of Neurological Death or Major Stroke through 365-day s ≥ 35.0% H_a: Incidence of Neurological Death or Major Stroke through 365-day s < 35.0% Success of the primary safety endpoint will be evaluated using a 1-tailed exact binomial test with a type 1 error rate of 2.5% based on Intention to Treat (ITT) population. Primary Effectiveness Endpoint: Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure H_o: Percentage of primary effectiveness endpoint through 365-day s ≤ 41.0% H_a: Percentage of primary effectiveness endpoint through 365-day s > 41.0% Success of the primary effectiveness endpoint will be evaluated using a 1-tailed exact binomial test with a type 1 error rate of 2.5% based on ITT population.	

	The primary presentation of the results will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. Results will be summarized using counts, percentages, and exact binomial confidence intervals. To claim study success, both primary safety and effectiveness endpoints should be met. The per-protocol population will be used for sensitivity analyses. Full details of the justification for the safety endpoint threshold and effectiveness endpoint threshold, along with reference literature, are provided in **Section 13**. **Interim Analysis and Sample Size Re-estimation** An adaptive sample size re-estimation approach will be used in this study. The interim assessment for evaluation of the sample size will be predicated on the primary effectiveness and primary safety endpoints and conducted using a conditional power (CP) approach as described by Mehta and Pocock (2011).[53] The interim assessment will be conducted when at least 50 subjects complete the 365-day evaluation or withdraw/die prior to the 365-day evaluation. The CP for both primary endpoints will be assessed. If the CP for at least one of the primary endpoints is too low, the sample size will not be increased. If the CP falls in a range defined as promising (30% ≤ CP < 80%), then the sample size will be increased up to a pre-determined upper limit in order to increase the CP up to the 80% level. The planned interim analysis will not permit early stopping for effectiveness.

3. Introduction

3.1. Background

Ruptured intracranial aneurysms (RIAs) are amongst the most dangerous cerebrovascular lesions, characterized by acute presentation and dismal natural history if not correctly diagnosed and treated promptly.[9,10,54] Approximately, 3% of the population harbors an unruptured intracranial aneurysm (UIA),[1] and as many as 29% of unruptured intracranial aneurysms (UIAs) were reported to rupture during a lifelong follow-up.[2] An estimated 30,000 people in the United States suffer an aneurysmal rupture each year.[3] In North America and globally, the crude incidence of aneurysmal subarachnoid hemorrhage (aSAH) due to ruptured aneurysms was reported to be 6.9[55] and 6.67[56] per 100,000 persons, respectively. Aneurysmal SAH challenges the healthcare system as it is associated with a high case fatality rate (range between 32% and 67%[11]), occurs at a relatively young age compared with other types of stroke, and many survivors are left in a functionally dependent state.[4-6] For patients with nontraumatic SAH in the United States, in-hospital mortality was reported for 25.3% - 45.4% of patients;[6,57,58] in surviving patients, major loss of function was reported for 61.8 %[57] and 66%[58] of patients, and 20-year prognosis for survival is significantly lower than for age- and sex-matched general population.[59] Additionally, not all RIAs are amenable to either clipping or coiling.[17-20,60]

During the historical era, only good-grade SAH patients and patients who recovered to good grade were candidates for treatment.[9] According to Korja et al., most common reasons for conservative management of aSAH were poor clinical grade on admission, anticipated operative challenges, death before planned treatment, patients considered too old for treatment and aneurysms too small for treatment.[9] Korja et al. and Nishioka et al. reported natural history of ruptured but untreated intracranial aneurysms[9,10] and found that during a lifelong follow-up of 510 untreated aSAH patients, the 1-year mortality rate was 65%, 5-year mortality 69%, and 10-year mortality 76%.[9] Out of the 568 cases of patients with aSAH reported to the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage from 1958 to 1965, 378 patients were found to have died and 40% of these deaths had occurred within 6 months of hemorrhage.[10] Mortality rates at 1-year among hospital-admitted patients with untreated RIAs was reported as high as 90% for poor-grade patients and 75% for good-grade patients admitted within a week and managed conservatively.[9]

Even in cases of ruptured aneurysms that were amenable to treatment such as surgical clipping and endovascular coiling, high mortality rates and poor outcomes have been reported. A tertiary care center reported that among 330 patients treated for aSAH, the mortality rates at discharge in the surgical clipping and endovascular coiling groups were 21.2% (65/307) and 17.3% (4/23), respectively.[6] Other sources report a mortality rate of 12% before receiving medical attention, an additional mortality of 40% within 1 month of admission to hospital, and 30% morbidity among the survivors.[61,62] Case fatality rates for treated aSAH patients range between 32% and 67%,[11] with the majority of studies in a review by Nieuwkamp et al., reporting case fatality rates of more than 40%.[5] Langham et al., in their study of SAH in 2397 patients

with aneurysm repair attempted in 2198 (91.7%) patients, reported an unfavorable outcome in 38.5% patients (34.6% in repaired and 81% in unrepaired patients) at 6 months follow-up.[8] Hamada et al., in their study from Japan, stated that out of the 1634 patients surgically treated for SAH with the exact location of the ruptured aneurysm confirmed in 1950 (92.2%) patients, only 70.6% had a good outcome, while out of the 477 conservatively treated patients, only 5.7% survived and 4.2% had a favorable outcome.[7]

Two most common causes of death among patients with RIAs are rebleeding or neurological deterioration due to the initial rupture. Nishioka et al. reported that the rate of probable recurrent bleeding after 6 months was 2.2% per year for the first 9.5 years and 0.86% per year for the second decade; reported rebleeding episodes were fatal in 78% patients.[10] Other studies also report that most patients die as a result of the initial bleed or its immediate complications.[11,63] Singh et al. reported that the most common cause of death among patients with aSAH at 3 months was progressive neurological deterioration followed by re-bleed of the aneurysm,[6] similar to the conclusion reached by other authors.[64,65] A subset of RIAs, ruptured blister aneurysms, involving the vertebrobasilar system have an extremely high rate of early rebleeding, up to 70% in some series, with the majority of the rebleeding events occurring within the first 24 hours after presentation and many associated with a poor clinical outcome.[54] Ruptured blister aneurysms of the internal carotid artery have a similar malignant course, with high rates of rebleeding before treatment and high rates of procedural rupture (up to 50% reported) during, and in some cases even after, surgical clipping.[66-70]

For the treatment of RIAs, deconstructive treatment such as endovascular trapping or parent artery occlusion is often an unacceptable or suboptimal treatment strategy, particularly in the setting of SAH. Patients with SAH are susceptible to cerebral vasospasm and delayed cerebral ischemia.[71] If the parent artery is deconstructed either surgically or with endovascular devices, subsequent cerebral vasospasm can compromise collateral flow[51] resulting in severe stroke. In addition, following deconstruction of the parent artery, the distal circulation becomes inaccessible to endovascular devices and distal vasospasm in the territory cannot be treated either with angioplasty or pharmacological infusion.[72] As such is it not surprising that in a large meta-analysis of the endovascular treatment of RIAs, deconstructive techniques were associated with a higher rate of peri-procedural ischemic stroke than reconstructive approaches.[72]

Reconstructive surgical treatment in ruptured aneurysms could be hazardous, as the vessel often lacks the structural integrity to hold aneurysm clips, leading to very high rates of intra-operative rupture and a high risk of parent vessel stenosis or occlusion.[54,66-68] A meta-analysis of 27 studies that included 11,568 patients (7,230 underwent surgical clipping, and 4,338 underwent endovascular coiling) concluded that coiling yields a better clinical outcome in RIAs than clipping.[12] Coiling leads to a greater risk of rebleeding and the risk of vasospasm is higher after clipping than coiling. The mortality of the 2 treatments showed no significant difference within 1 year.[12] Of endovascular treatment modalities used to treat RIAs, coiling, balloon-assisted coiling (BAC) or stent-assisted coiling (SAC) are used in 97.8% of cases,[73] and are associated with lower mortality (17.3%[6,57]) and disability (23.7%-33.1%[34,74,75]) than surgical clipping.

However, reconstructive endovascular treatment using a traditional strategy of coil embolization may not be optimal for all cases if a well-defined saccular component of the aneurysm either does not exist or is too small to safely accommodate the introduction of coils, or if the parent vessel is friable with circumferential involvement of the wall over a relatively long segment of the vessel.[13] The thin, fragile walls and poorly defined neck make ruptured blister aneurysms challenging lesions to treat with simple coiling or clipping, with not negligible rates of intraoperative aneurysm rupture.[14] The lack of a true neck in the dissecting/fusiform aneurysms usually renders coiling and clipping impossible in cases of ruptured aneurysms.[15] In addition, embolization of wide-neck and wide-neck bifurcation aneurysms without the use of adjunctive devices is difficult because of the instability of the coil mass.[16]

For these reasons, endovascular reconstruction of the diseased segment with stents has gained increasing acceptance due to lower rate of recurrence[23] and procedure-related mortality.[24] This was first accomplished with balloon-expandable coronary stents and then subsequently with the available coil-assisted stents, placed as stand-alone devices in an attempt to reinforce the diseased segment. Zhang et al. suggest that flow diverters provide a more robust hemodynamic effect compared with conventional stents.[23] The implanted construct such as a flow diverter, works by diverting the flow away from the aneurysm, promoting progressive intra-aneurysmal thrombosis, leading to neoendothelialization[76-78] and resolution of complex lesions.[16] During implantation of stents or flow diverters within an intracranial artery, it is recommended that antiplatelet agents should be administrated and maintained postoperatively to prevent in-stent thrombosis and subsequent ischemic events.[79] Stent based endovascular treatment of aSAH due to RIAs necessitate the use of antiplatelet therapy for two reasons: introduction of a permanent implant in the normal artery in itself is thrombogenic[80] and patients with SAH are also in a prothrombotic state.[80-82] These two factors likely account for the dramatically higher rate of thromboembolic events with stent-assisted coiling for acutely ruptured aneurysms. Preprocedural administration of antiplatelet medications might reduce the risk of thromboembolic complications during stent-assisted coiling of RIA,[83] since majority of thromboembolic complications are known to occur intra-operatively.[84]

The Pipeline™ Embolization Device, which is a flow diverter, represents a promising treatment option for the treatment of RIAs.[85] The low porosity and high mesh density of flow diverters facilitate aneurysmal occlusion by reducing the blood flow into the aneurysms and by serving as a scaffold for endothelialization across the aneurysm neck leading to progressive occlusion and reduced rates of recanalization of the treated aneurysm[86] due to progressive thrombosis and shrinkage of the lesion.[87] A meta-analysis of 20 studies by Cagnazzo et al. that included 223 patients with acutely ruptured intracranial aneurysms treated with flow diverters reported that even though only 32% of the ruptured aneurysms were occluded immediately after treatment, nearly 90% of the lesions had complete/near-complete occlusion during the 9.6 months of radiologic follow-up, with slightly higher occlusion rate (89%) for blister and dissecting/fusiform aneurysms compared with saccular lesions (79%).[16] Another meta-analysis by Madaelil et al. reported that 81% of patients with ruptured aneurysms treated with flow diverters had

favorable clinical outcomes,[21] which is comparable to the number of patients with similar outcomes in large studies such as the International Subarachnoid Aneurysm Treatment (ISAT).[88] Cagnazzo et al. reported 17.8% flow diversion associated complications which mostly occurred in the periprocedural/early period after treatment, with a 7% treatment-related morbidity,[16] and Madaelil et al. reported composite rate of hemorrhagic or ischemic complication as 12%.[21] Cagnazzo et al. reported hemorrhagic complications in 7% of the patients[16] and Madaelil et al. reported a 9% composite rate of intracranial hemorrhagic complications in the meta-analysis, including 5% from aneurysm re-rupture and 4% from other causes.[21] Ischemic complications rates were reported to be 8%[16] and 4%.[21] Madaelil et al. suggested that flow diverter treatment may be more effective for small ruptured aneurysms.[21] Flow diverters may present a viable treatment option for RIAs that are not readily amenable to first-line treatments such as coil embolization or surgical clipping,[21] or when traditional treatment methods are unfeasible.[16,22] Recently, AlMatter et al. reported a study of 45 consecutive cases of acutely ruptured intracranial aneurysms where flow diversion was performed after a median of 4 days.[22] The authors reported procedural complication rate of 13.3% that resulted in 2.2% permanent morbidities and 4.4% mortalities.[22] Immediate complete occlusion was achieved in 13.3% and among survivors, complete occlusion was achieved in 94.6%; excellent clinical outcome was recorded in 68.9% and 81.6% of the total population and survivors, respectively.[22] No major hemorrhagic complications related to antiplatelet therapy were recorded and there were no records of rebleeding.[22] Although there are multiple publications describing the use of flow diverters[16,21,22] including Pipeline™ Shield Device[22,40,51,52] in RIAs, no structured, prospective, externally monitored and independently adjudicated study of the Pipeline™ family of devices (or any flow diverter) for the treatment of RIAs has been performed. Especially, there are no studies looking at flow diverters in aneurysms that are acutely ruptured, wide- neck, and not amenable to surgical clipping and coiling alone.

Although antiplatelet therapy is recommended in patients implanted with stents or flow diverters, recent studies differ considerably on the antiplatelet therapy regimen for endovascular treatment of patients with RIAs[21,89-92] and there is little consensus on the therapeutic regimen to be followed for antiplatelet administration that minimizes complications in stent-assisted coiling of RIAs.[83] Based on currently available data, it appears that standardization for antiplatelet therapy for endovascular treatment of ruptured aneurysms is needed.[16,21,22]

Published data on the Pipeline™ Embolization Device used to treat complex large/giant aneurysms show rates of 68% - 94.4% complete occlusion that remains persistent 2-3 years after the index procedure and 0.0% - 13.9% associated morbidity and 0.0% - 6.9% mortality.[32,33,93-97] Technical results of the Pipeline™ Flex Device showed high procedural success (93% - 100%).[98-103] Additionally, the Pipeline™ Flex Device was associated with significant reductions in total procedure time, fluoroscopy time, patient radiation exposure, contrast usage, and rate of deployment failure compared with the Pipeline™ Embolization Device.[104]

However, Pipeline™ Embolization Device still has associated risks such as ischemic complications, including the risk of thromboembolism and stenosis.[35-38] These risks may be due to the high surface area of metal coverage of Pipeline™ Embolization Device (metal coverage higher than that of self-expanding stents).[35-38] A meta-analysis that reviewed > 1700 aneurysms treated with flow diverters found that ischemic complications were reported in most of the included studies with an overall mean rate of 4.1% (range: 1% - 14.2%) and significant stenosis being reported at an overall rate of 6.8% (range: 0% - 18%).[38] Thus, to reduce ischemic and stenosis complications, it is expected that new generation flow diverters incorporate modifications to existing flow diverters.[39-41]

Thromboembolic complications (e.g. thrombosis) can result due to surface activation (vascular endothelial/vessel wall injury), disruption of blood flow, or alterations in the constitution of the blood (hypercoagulability) based on the principles of Virchow's triad.[42] The Virchow's triad is applicable irrespective of vessel bed location. Of the three contributing factors for the thromboembolic complications, surface or contact activation is influenced by device material.[42] Flow diverters which are implanted intraluminal typically have high metal coverage (30-35%) may therefore contribute to material contact activation. Continued improvement of the Pipeline™ family of devices resulted in the development of the third-iteration flow diverter, Pipeline™ Shield Device, to address surface activation due to device materials (material thrombogenicity).

Shield Technology™ utilizes a phosphorylcholine (PC) surface modification to the existing implant combined with the Pipeline™ Flex Device delivery system. The Shield Technology™ surface modification applied to the implant is a well-understood, inert, non-biodegradable, synthetic PC polymer material that is chemically bonded to the braid surface. The polymer is a chemically derived material, created to mimic the outer membrane of a human red blood cell. Shield Technology™ reduces the material thrombogenicity of the braid surface compared to the bare metal Pipeline™ Flex Device implant based on bench data with human platelets and plasma.[43-50] In vitro assessment of stainless steel with PC-surface modification demonstrated that it is resistant to fibrinogen absorption, platelet activation, platelet adherence, and erythrocyte adherence.[105,106] Platelet adherence and thrombosis are also inhibited on PC-coated stents implanted in peripheral arteries of rabbits, pigs, dogs, and baboons.[105,107-109] Nine published pre-clinical studies analyzed thrombogenicity, endothelialization, stenosis, and aneurysm occlusion for the Pipeline™ Shield Device.[110-118] Three of these studies[110,111,117] compared thrombogenicity of the Pipeline™ Shield Device to other flow diverters such as Pipeline™ Embolization Device,[111] Pipeline™ Flex Device,[110,117] SILK+,[110] P64, Derivo®,[117] and Flow Redirection Endoluminal Device (FRED™)[110,111] in vitro under varied antiplatelet regimens. Overall, the published in-vivo preclinical studies demonstrated that the Shield Technology™ resulted in reduced thrombus formation and in-stent stenosis; while demonstrating similar occlusion and faster and more uniform healing response as compared to the previous generations of Pipeline™ Embolization Device and other flow diverters. AlMatter et al. opined that the surface modification to reduce the inherent thrombogenicity of flow diverters is a promising recent advancement.[22]

The SHIELD OUS (**Section 3.3.2.1**) and PFLEX (**Section 3.3.2.2**) prospective, multicentre, post-market studies were carried out to gather real-world safety and effectiveness data of the Pipeline™ Shield Device. These studies, combined, gathered substantial real-world evidence on more than 250 subjects. Both SHIELD OUS and PFLEX studies achieved a high rate of complete aneurysm occlusion with the use of the Pipeline™ Shield Device in the treatment of intracranial aneurysms. The incidence of major stroke, neurological death, and delayed intracerebral hemorrhage in both these studies were low. Therefore, results from the SHIELD OUS and PFLEX studies demonstrated that the Pipeline™ Shield Device is effective and safe for the endovascular treatment of intracranial aneurysms (**Section 3.3.2.1** and **3.3.2.2**).

3.2. Pre-clinical Summary

3.2.1. Summary of Animal Studies

3.2.1.1. 7 Day Porcine Study Summary

This study was designed to evaluate the device interaction with vessel wall and corresponding tissue response of the Pipeline™ Shield Device as compared to the Pipeline™ Flex Device at 7 days. Six animals were successfully implanted with up to three paired test and control braids (6 total devices). All animals survived to their designated time point.

With respect to the assessments of overall animal health, and the results of the vascular response and histopathological analyses, this study has met the three protocol-specified success criteria. No safety risks were identified with the Pipeline™ Shield Device when compared to the Pipeline™ Flex Device. Furthermore, there were no major acute and/or sub-acute complications during implant and throughout in-life up to the 7-day survival time point. The pathology findings of this study are supportive of an acceptable safety profile for all braids and delivery systems, with no risks to patients identified.

3.2.1.2. 13 Week Rabbit Study Summary

A 13-week evaluation of the Pipeline™ Shield Device was performed in a rabbit elastase model. The study assessed the safety and vascular compatibility of the device when deployed over the neck of aneurysms in the carotid arteries and across the ostia of lumbar arteries in the descending aorta of 19 New Zealand rabbits. Results showed that the Pipeline™ Shield Device was non-inferior to Pipeline™ Flex Device in terms of safety and was comparable in terms of aneurysm occlusion. There was also no significant device migration noted with the Pipeline™ Shield Device.

Taken together, the results show that the Pipeline™ Shield Device is safe and efficacious in this animal model.

3.2.1.3. 52 Week Rabbit Study Summary

This study is designed to assess safety and vascular compatibility of the Pipeline™ Shield Device compared to the Pipeline™ Flex Device when deployed over the neck of elastase-induced aneurysms in rabbit carotid arteries and across the ostia of lumbar arteries in the descending aorta (DAo) of the rabbit model.

In this study, fourteen (14) animals completed the study at the intended termination time point of 365 days (actual 363-364 days). The Pipeline™ Shield Device was shown to be non-inferior to the Pipeline™ Flex Device in terms of all acceptance criteria, including clinically significant thromboembolic events, clinically significant parent vessel dissection, clinically significant (i.e. > 50% stenosis) parent vessel occlusion, clinically significant (i.e. > 50% stenosis) side branch vessel occlusion, vascular response, incidence of significant device migration, and aneurysm occlusion rates. Taken together these findings indicate the safety and efficacy of the Pipeline™ Shield Device and equivalence to the Pipeline™ Flex Device in this animal model at 1 year.

3.3. Clinical Experience with the Pipeline™ Device

The clinical benefits achieved with the use of Pipeline™ Embolization Device have been consistently demonstrated in multiple studies.[30,32,78,93,94,96,97,119-122] Pipeline™ Embolization Device demonstrates high efficacy and a good safety profile in treating aneurysms of diverse morphology, ranging from small to more complex and difficult to treat aneurysms (e.g. large aneurysms, wide-necked aneurysms, or aneurysms with complex morphology).[32,33,94,123-125] Clinical outcomes from 6 key studies with earlier generations of the Pipeline™ Device as well as 2 studies with the Pipeline™ Shield Device, sponsored by Medtronic, are summarized below.

3.3.1. Clinical Experience with Earlier Generations of the Pipeline™ Device

3.3.1.1. PITA: Pipeline™ for Intracranial Treatment of Aneurysms

The PITA study was the first prospective multicenter study of a flow-diverting construct for the treatment of complex intracranial aneurysms. Thirty-one subjects with wide-necked (> 4 mm) and unfavorable dome/neck ratios (< 1.5 mm) and subjects with an intracranial aneurysm that had failed previous endovascular treatment were included. Of the 31 aneurysms, 65% were small (< 10 mm) and the remaining 35% were large and giant in size. In total, 46 out of 47 (97.9%) Pipeline™ Device braids were placed successfully. In 30 out of 31 subjects, the entire neck of the targeted intracranial aneurysm was covered by the Pipeline™ Device braid. Complete aneurysm occlusion was observed in 93.3% (28/30) subjects at 180 days. Two subjects experienced a major peri-procedural stroke and no deaths occurred.

3.3.1.2. PUFs: Pipeline™ Embolization Device for Uncoilable or Failed Aneurysms

The PUFs study was a multicenter, prospective, single-arm study to evaluate the safety and effectiveness of the Pipeline™ Embolization Device in complex large and giant intracranial aneurysms. One hundred

seven subjects with large and giant unruptured wide-necked aneurysms in the petrous to the superior hypophyseal segment of the ICA were treated with the Pipeline™ Embolization Device. The aneurysms measured ≥ 10 mm in diameter and had either a neck ≥ 4 mm or no discernable neck. A total of 104 subjects with 106 aneurysms were included in the primary effectiveness cohort and evaluated by an independent core lab. Of the 106 aneurysms, 78 demonstrated complete occlusion without major stenosis at 180 days (73.6%; 95% posterior probability interval: 64.4% to 81.0%). At 1-year, 86.8% (79/91) of the target aneurysms were completely occluded. This rate increased to 95.2% (59/62) complete occlusion at 5 years. There were no cases of aneurysm recurrence. The primary safety endpoint was the occurrence of major ipsilateral stroke or neurologic death at 180 days, which occurred in 6 of the 107 subjects (5.6%; 95% posterior probability interval: 2.6% to11.7%). At the 5-year follow-up, the rate of major ipsilateral stroke or neurologic death remained at 5.6% (6/107).[126]

3.3.1.3. IntrePED: International Retrospective Study of the Pipeline™ Embolization Device

The IntrePED study was a retrospective, global, post-market study of subjects treated with the Pipeline™ Embolization Device at 17 centers worldwide.[30,34] A total of 793 subjects with 906 aneurysms of various sizes and locations were included. The median follow-up period was 19.3 months with 89% of the subjects with greater than 1-year follow-up. The overall neurological morbidity rate was 7.4% (59/793) and the neurological mortality rate was 3.8% (30/793). The combined neurological morbidity and mortality rate was 8.4% (67/793). The combined neurological morbidity and mortality for the subset of subjects with unruptured aneurysms was lower at 7.5% (54/720). IntrePED provided data on the safety of the Pipeline™ Embolization Device in the treatment of various intracranial aneurysms in a real-world clinical setting.

3.3.1.4. ASPIRe: Aneurysm Study of Pipeline™ in an Observational Registry

ASPIRe was a prospective, multicenter, single-arm, post-market registry of 191 intracranial aneurysm patients with 207 aneurysms from 28 worldwide centers who underwent treatment with the Pipeline™ Embolization Device. The 207 aneurysms in the study had a median follow-up duration of 6.6 months. The majority of the aneurysms treated were saccular and overall average size was 14.5 mm.

Neurological morbidity was 6.8% (13/191) and the neurological mortality rate was 1.6% (3/191). The combined rate of neurological morbidity and mortality was 6.8% (13/19), with the most common major adverse event of interest being intracerebral hemorrhage (3.7%, 7/191) followed by ischemic stroke (1.6%, 3/191). Most of the major adverse events (6.3%, 12/191) occurred in the early post-operative phase within the first 30 days following Pipeline™ Embolization Device treatment.

Aneurysm occlusion was assessed for all subjects with imaging follow-up of at least 6 months by an independent Core Lab according to the Raymond-Roy scale. The median follow-up duration was 7.8 months and complete occlusion was reported in 75% of subjects (77/103).

The ASPIRe registry, as a comprehensive evaluation of Pipeline™ Embolization Device use in the real world, confirmed that the Pipeline™ Embolization Device is safe when used for the treatment of intracranial aneurysms in routine clinical practice, reporting a 6.8% rate of associated major morbidity and neurological mortality.

3.3.1.5. PREMIER: Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline™ Device

PREMIER was the first prospective, multicenter study to evaluate the use of the PED and Pipeline™ Flex Device for the treatment of small and medium, unruptured aneurysms of the internal carotid artery (ICA) and proximal vertebral artery (VA). The study was conducted in 1 Canadian and 22 U.S. centers.

A total of 141 subjects with 141 target aneurysms were treated in the study; target aneurysm was defined as the largest aneurysm treated in the procedure. The majority of target aneurysms (96.5%, 136/141) were unruptured at the time of entry into the study, while the remaining 5/141 aneurysms had been previously ruptured. The target aneurysms were mostly located in the ICA (95.0%, 134/141), most of which were located in C6 (ophthalmic segment, 74.6%, 100/134) and C7 (communicating segment, 14.2%, 19/134). Five percent (7/141) of aneurysms were located in the VA. The mean dome-to-neck ratio was 1.1 ± 0.28 and the mean aneurysm size was 5.0 ± 1.92 mm. Of the 141 target aneurysms, 119 (84.4%, 119/141) were small (< 7 mm) and 22 (15.6%, 22/141) were medium (7-12 mm) aneurysms. No large or giant aneurysms (≥ 13 mm) were included in the PREMIER Study.

Subject follow-up rates were high, with 98.6% (139/141) of subjects completing the 1-year clinical follow-up. Complete aneurysm occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm 1-year post-procedure (primary effectiveness endpoint) occurred in 76.71% of subjects. Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure (primary safety endpoint) occurred in 2.17% of subjects. A total of 81.9% (113/138) aneurysms had complete occlusion, none (0.0%; 0/138) had aneurysm recurrence and 2.9% (4/139) had aneurysm retreatment at the 1-year follow-up; residual neck was seen in 2.2% (3/138) of subjects, and residual aneurysm was seen in 15.9% (22/138) of subjects. There were no major strokes in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications. Delayed intracerebral hemorrhage > 30 days through 1-year post-procedure occurred in 0.73% of subjects. The overall mortality rate was 0.7% (1/141).

Overall, a high rate of complete aneurysm occlusion was achieved with the use of the Pipeline™ Device in the treatment of small/medium-sized wide-necked aneurysms. The incidence of major stroke, neurological death, and delayed intracerebral hemorrhage in the PREMIER study were low. Therefore, results from the PREMIER Study demonstrated that the Pipeline™ Device is effective and safe for the endovascular treatment of unruptured, small and medium, wide-necked intracranial aneurysms in the ICA and proximal VA.

3.3.1.6. INSPIRE: Innovative Neurovascular Product Surveillance Registry

INSPIRE is a neurovascular registry of patients treated for either intracranial aneurysms or large vessel occlusion-acute ischemic stroke (LVO-AIS) with a Medtronic market-approved device. INSPIRE aims to continuously assess safety and measure effectiveness of market-released neurovascular products. Additionally, the cumulatively collected high volume of patient data drives therapy evidence to support treatment paradigms in the rapidly evolving neurovascular therapy field. The objectives of the study are to identify unforeseen adverse events and potential signals for emerging performance issues, characterize patient outcomes and patterns of product use, and determine predictors of performance and effectiveness. Study endpoints are specific to each device; and include safety endpoints adjudicated by the Clinical Events Committee and effectiveness endpoints measured by an independent Core Lab. INSPIRE was launched in December 2016; 1009 patients with intracranial aneurysms were treated with the Pipeline™ Flex Device (N=242), Pipeline™ Shield Device (N=530), or Pipeline™ Vantage Embolization Device with Shield Technology™ (N=237) through March 1, 2022. Patients were enrolled from 37 neurointerventional centers across Europe, Asia, Australia, Latin America, Middle East and Russia. INSPIRE is the neurovascular arm of a larger global Medtronic Product Surveillance Registry (PSR) Platform which builds on more than 25 years of post-market clinical surveillance experience. Currently, INSPIRE is in the data collection stage.

3.3.2. Clinical Experience with Pipeline™ Shield Device

3.3.2.1. SHIELD OUS: Pipeline™ Flex with Shield Technology™ Embolization- An International Multicenter Observational Post Market Study of Treated Intra Cranial Aneurysms

The primary objective of the SHIELD Study was to assess the outcomes of the Pipeline™ Shield Device in subjects undergoing treatment for intracranial aneurysms in a real-world, post-market setting. The SHIELD study, conducted in 21 investigational sites outside the United States (OUS) which included European Union (EU), Australia and Israel, prospectively consented 205 subjects and attempted to treat a total of 204 target aneurysms in 204 subjects. The aneurysms were located in the parent arteries of the internal carotid artery (ICA segments C1-C7) (76.0%, 155/204), middle cerebral artery (MCA) (7.8%, 16/204), vertebral artery (VA) (6.4%, 13/204), Anterior Communicating Artery (AcoA) (5.9%, 12/204), and anterior cerebral artery (ACA) (3.9%, 8/204). The majority of aneurysms were located in the ICA (76.0%, 155/204), most of which were located in C6 (ophthalmic segment, 41.2%, 84/204) and C7 (communicating segment, 19.1%, 39/204). Of the 204 target aneurysms, 50.0% (102/204) were small (< 7 mm), 33.8% (69/204) were medium (7-12 mm), 13.7% (28/204) were large (13-24 mm), and 2.5% (5/204) were giant (≥ 25 mm). The majority of target aneurysms (81.4%,166/204) were never ruptured at the time of entry into the study, while previously ruptured target aneurysms were reported as acutely ruptured (< 30 days) in 1.5% (3/204) and as previously ruptured > 30 days in 16.7% (34/204); rupture status was not reported in the remaining

0.5% (1/204) of target aneurysms. Device deployment success on a subject level was observed in 98.0% (200/204) of subjects.

In the SHIELD Study, follow-up visits were not required by the Clinical Investigation Plan and only conducted per standard of care at the investigational site. In the study population, 87.3% (178/204) subjects returned for the 30-day follow-up visit, 81.4% (166/204) subjects returned for the 3-month follow-up visit, 91.2% (186/204) subjects returned for the 6-month follow-up visit, and 83.8% (171/204) subjects returned for the 1-year follow-up visit. Complete aneurysm occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm 1-year post-procedure (primary effectiveness endpoint) occurred in 71.67% of subjects. A total of 75.0% (141/188) subjects had complete target aneurysm occlusion, 0.0% (0/204) subjects had aneurysm recurrence and 2.0% (4/200) subjects had aneurysm retreatment through 1-year follow-up; residual neck was seen in 4.8% (9/188) of subjects and residual aneurysm was seen in 20.2% (38/188) of subjects. Through 1-year follow-up, majority of subjects (98.94%, 186/188) did not have significant stenosis, defined as > 50% stenosis of the parent artery.

Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure (primary safety endpoint) occurred in 3.23% of subjects. Major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications were observed in 2.9% (6/204) of subjects. No delayed intracerebral hemorrhage (> 30 days to 1-year post-procedure) was observed (0.0%). Overall, the incidence of major stroke, neurological death, and delayed intracerebral hemorrhage in the SHIELD study was low. Through the 1-year follow-up, the rate for death was 1.0% (2/204) (same for neurological death), all stroke was 6.4% (13/204), disabling stroke as observed (including death) was 1.0% (2/200), and ICH was 4.4% (9/204). Summary of primary endpoints of SHIELD study is presented in **Table 3-1**.

Table 3-1. Summary of Primary Endpoints of SHIELD Study

Endpoints	Rates	2-sided 95% exact binomial confidence interval
Primary Effectiveness Endpoint: Complete aneurysm occlusion (defined as Raymond-Roy grade 1[127]) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure		
FAS# population (N=200)	72.35%	(65.68%, 78.37%)
ICA†-FAS population (N=149)	76.24%	(68.59%, 82.82%)
Primary Safety Endpoint: Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure		
ITT* population (N=204)	3.23%	(1.27%,6.68%)
ICA† population (N=153)	3.27%	(1.07%,7.46%)

*Intention to Treat (ITT) population includes all consented subjects in whom deployment of the Pipeline™ Shield Device was attempted. For the ITT population, primary effectiveness endpoint analysis was based on Full Analysis Set (FAS) population and safety analysis was based on the ITT population.
#Full Analysis Set (FAS) is defined as a subset of the ITT population including only those in whom the Pipeline™ Shield Device was implanted.

†Internal Carotid Artery population (ICA population) is defined as a subset of ITT population that included only those subjects in whom the Pipeline™ Shield Device was implanted in the ICA (segments C2-C7). For the ICA population, primary effectiveness endpoint analysis was based on FAS (referred to as ICA-FAS) and safety analysis was based on the ICA population.

Overall, a high rate of complete aneurysm occlusion was achieved with the use of the Pipeline™ Shield Device in the treatment of intracranial aneurysms. The incidence of major stroke, neurological death, and delayed intracerebral hemorrhage in the SHIELD study were low. Therefore, results from the SHIELD study demonstrated that the Pipeline™ Shield Device is effective and safe for the endovascular treatment of intracranial aneurysms.

In summary, wide-necked aneurysms are poor candidates for endovascular treatment with coils and along with the possibility of coil protrusion into the parent vessel, there are reportedly high rates of aneurysm recurrence or recanalization after treatment.[128-131] Current evidence demonstrates that the Pipeline™ Device meets the need for the treatment of wide-necked intracranial aneurysms and results in high complete occlusion rates, low recurrence rates and a favorable safety profile.

3.3.2.2. PFLEX: Pipeline™ Flex Embolization Device with Shield Technology™ Clinical Study

The primary objective of the Pipeline™ Flex Embolization Device with Shield Technology™ Clinical Study (PFLEX) was to assess the outcomes of Pipeline™ Shield Device in patients undergoing treatment for intracranial aneurysms in a real-world, post-market clinical setting. The PFLEX study was conducted in 7 European Union study centers which prospectively consented 58 subjects and attempted to treat a total of 50 target aneurysms in 50 subjects. Ninety-four percent (47/50) of target aneurysms were located in the intracranial ICA (C2 to C7 including the terminus), and 6.0% (3/50) of aneurysms were located in the vertebral artery. Most target aneurysms (48.0%, 24/50) were small (< 7 mm), 30.0% (15/50) were medium (7- < 13 mm), 20.0% (10/50) were large (13- < 25 mm), and 2.0% (1/50) were giant aneurysms (≥ 25mm). Most subjects (88.0%, 44/50) had unruptured target aneurysms at the time of entry into the study, and 6 (12.0%, 6/50) subjects had previously ruptured aneurysms (> 30 days) which were treated in this study. None of the subjects had previously ruptured aneurysms acutely (< 30 days from the study). Device deployment success on a subject level was observed in 100% (50/50) of subjects.

In the PFLEX Study, subject follow-up rates were high, with 6-month clinical follow-up data available for 98.0% (49/50) and 1-year clinical follow-up data available for 98.0% (49/50) of subjects for analysis of safety endpoints. Complete aneurysm occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm 1-year post-procedure (primary effectiveness endpoint) occurred in 73.62% of subjects. A total of 78.7% (37/47) subjects had complete occlusion of their target aneurysms and none (0%) had aneurysm recurrence or retreatment through the 1-year follow-up; residual neck was seen in 4.3% (2/47) of subjects, and residual aneurysm was seen in 17.0% (8/47) of subjects. Through 1-year follow-up, majority of subjects (95.7%, 45/47) did not have significant parent artery stenosis, defined as > 50% stenosis of the parent artery.

Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure (primary safety endpoint) occurred in 0.0% of subjects. There were no major strokes in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications. There was no delayed intracerebral hemorrhage > 30 days through 1-year post-procedure (0.0%; 0/50). The overall mortality rate was 0.0% (0/50). Summary of primary endpoints of PFLEX study is presented in **Table 3-2**.

Table 3-2. Summary of Primary Endpoints of PFLEX Study

Endpoints	Rates	1-Sided 97.5% Exact Binomial Confidence Interval
Primary Effectiveness Endpoint: Complete aneurysm occlusion (defined as Raymond-Roy grade 1[127]) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure		
ITT‡ population (N=50)	73.62%	59.39%*
ICA# Population (N=47)	74.23%	59.24%*
Primary Safety Endpoint: Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure		
ITT‡ population (N=50)	0.0%	7.1%†
ICA# population (N=47)	0.0%	7.5%†

*Lower Bound of the Binomial Confidence Interval
†Upper Bound of the Binomial Confidence Interval
‡Intention to Treat (ITT) population included all consented subjects in whom deployment of the Pipeline™ Shield Device was attempted.
#Internal Carotid Artery Population (ICA Population) is defined as a subset of ITT population that included only those subjects in whom the Pipeline™ Shield Device was implanted in the ICA (segments C2-C7 including the terminus).

Overall, a high rate of complete aneurysm occlusion was achieved with the use of the Pipeline™ Shield Device in the treatment of intracranial aneurysms. The incidence of major stroke, neurological death, and delayed intracerebral hemorrhage in the PFLEX study were low. Therefore, results from the PFLEX Study demonstrated that the Pipeline™ Shield Device is effective and safe for the endovascular treatment of intracranial aneurysms.

3.4. Published Literature on Treatment of Ruptured Aneurysms with Flow Diversion

Traditional treatments of RIAs such as conservative management, surgical clipping and endovascular coiling either have poor outcomes and high mortality, or are suboptimal or even impossible treatment strategies due to aneurysm morphology of RIAs and characteristics of the vessel wall.[9,10,14-16,72] Therefore, treatment of RIAs with flow diverters is receiving increased attention and acceptance.[16,21,22]

A meta-analysis of 20 studies by Cagnazzo et al. that included 223 patients with acutely ruptured intracranial aneurysms treated with flow diverters reported that even though only 32% of the ruptured aneurysms were occluded immediately after treatment, nearly 90% of the lesions had complete/near-complete occlusion during the 9.6 months of radiologic follow-up, with slightly higher occlusion rate (89%) for blister and dissecting/fusiform aneurysms compared with saccular lesions (79%).[16] Another meta-

analysis by Madaelil et al. reported that 81% of patients with ruptured aneurysms treated with flow diverters had favorable clinical outcomes,[21] which is comparable to the number of patients with similar outcomes in large studies such as ISAT.[88] Cagnazzo et al. reported 17.8% flow diversion associated complications which mostly occurred in the periprocedural/early period after treatment, with a 7% treatment-related morbidity,[16] and Madaelil et al. reported composite rate of hemorrhagic or ischemic complication as 12%.[21] Cagnazzo et al. reported hemorrhagic complications in 7% of the patients[16] and Madaelil et al. reported a 9% composite rate of intracranial hemorrhagic complications in the meta-analysis, including 5% from aneurysm re-rupture and 4% from other causes.[21] Ischemic complications rates were reported to be 8%[16] and 4%.[21] Madaelil et al. suggested that flow diverter-based treatment may be more effective for small aneurysms.[21] Flow diverters may present a viable treatment option for RIAs that are not readily amenable to first-line treatments such as coil embolization or surgical clipping,[21] or when traditional treatment methods are unfeasible.[16,22] Recently, AlMatter et al. reported a study of 45 consecutive cases of acutely ruptured intracranial aneurysms treated with flow diverters that resulted in a procedural complication rate of 13.3% (2.2% permanent morbidities and 4.4% mortalities) and immediate complete occlusion rate of 13.3%. Among survivors, complete occlusion was achieved in 94.6%; excellent clinical outcome was recorded in 68.9% and 81.6% of the total population and survivors, respectively.[22] No major hemorrhagic complications related to antiplatelet therapy were recorded and there were no records of rebleeding.[22]

Although there are multiple publications describing the use of flow diverters[16,21,22] and the Pipeline™ Shield[22,40,51,52] Device in RIAs, no structured, prospective, externally monitored and independently adjudicated study of the Pipeline™ family of devices (or any flow diverter) for the treatment of RIAs has been performed. Especially, there are no studies looking at flow diverters in aneurysms that are acutely ruptured, wide- neck, and not amenable to surgical clipping and coiling alone. Additionally, while the above referenced three studies[16,21,22] with flow diverters provide outcomes on ruptured aneurysms, it is important to note that these are not specifically wide- neck aneurysms not amenable to surgical clipping and coiling alone.

Below sub-sections summarize the published literature on the Pipeline™ Embolization Device (**Section 3.4.1**) and on Pipeline™ Shield Device (**Section 3.4.2**) for treatment of ruptured aneurysms.

3.4.1. Pipeline™ Embolization Device (Pipeline™ Embolization Device and Pipeline™ Flex Device) for Treatment of Ruptured Aneurysms

In their review of endovascular treatment of RIAs, Zhang et al. suggested that flow diverters provide a more robust hemodynamic effect compared with conventional stents,[23] and tend to achieve improved occlusion rates at immediate and follow-up angiography,[132,133] but periprocedural complication rate seemed to be higher, especially thromboembolic complications, with comparable clinical outcomes.[23] Improved antiplatelet therapy for acute RIAs might reduce the thromboembolic and hemorrhagic complication rate.[23]

Twenty (20) studies reported use of the Pipeline™ Embolization Device for treatment of patients with acutely ruptured aneurysms.[30,48,134-151] One study specifically focused on treatment of ruptured aneurysms,[134] and 2 studies reported treating a single patient each in an acute SAH setting.[135,146] In the other 17 studies, patients with ruptured aneurysms represented 5.9%-20% of patients.[30,48,136-145,147-151] Overall, these studies on 2,542 patients with 2,763 intracranial aneurysms reported on treatment of 217 ruptured aneurysms.[30,48,134-151]

Lin et al. (2016)[134] reported on the use of the Pipeline™ Embolization Device for treatment of 26 ruptured aneurysms in 26 patients. At median follow up of 5.9 months the study reported complete occlusion of 78.3% (18/23) of aneurysms, including all 8 blister aneurysms. Good clinical outcome (mRS ≤ 2) at a mean follow-up of 10.1 months was reported for 76.9% (20/26) of patients. Periprocedural complications occurred in 19.2% (5/26) of cases, including 2 asymptomatic complications and 3 deaths. Hemorrhagic complications were reported in 3.8% (1/26) of patients, and ischemic complications in 2 patients (1 procedure-related ischemic stroke that led to death, and 1 delayed asymptomatic ischemic stroke). Overall mortality was 11.5% (3/26), with two deaths reported as treatment-related. The study concluded that the Pipeline™ Embolization Device can be utilized for ruptured aneurysms and is a good option for blister-type aneurysms. However, due to periprocedural complications, it should be reserved for lesions that are difficult to treat by conventional clipping or coiling.[134] Of the 5 studies presenting subgroup analyzes of pooled IntrePED, PUFS, and ASPIRe population,[30,140,143,151,152] one study reported that the rate of ischemic complications in patients with ruptured aneurysms (5.4%, 4/74) was not significantly different from patients with unruptured aneurysms (4.5%, 32/719).[140] The other study reported that the mortality rate for this cohort was 10.5% (8/76) of patients.[30] The other studies reported complete aneurysm occlusion for 6 out of 8,[138] 9 out of 11,[139] 2 out of 2,[142] and 5 out of 6[144] of ruptured aneurysms at 5.9 - 11.5 month follow-up. Good clinical outcome (mRS ≤ 2) was reported for 70% - 80%,[48,138,141] and all of 2,[142] 2,[147] and 7[144] patients. One study reported mRS decline in 5 of 11 patients; however, overall median postoperative mRS score was 0 with interquartile range (IQR) 1 and remained unchanged at the last follow-up. The presence of a ruptured aneurysm at the time of presentation was not significantly associated with mRS score decline on multivariate analysis.[139] Four of the studies reported either no mortality[139,144,147] or no procedure-related mortality[141] in the ruptured aneurysm cohorts. One study reported that a single patient of 10 diagnosed with SAH who underwent Pipeline™ Embolization Device placement died 21 days after the procedure;[137] and one study reported that 2 out of 10 patients died perioperatively due to severe SAH, with no device-related mortality.[138]

Additionally, four other studies/case reports specifically stated that treatment of RIAs with the Pipeline™ Embolization Device was feasible treatment option that was safe and effective, and/or led to good clinical outcomes. Linfante et al., in a study of 10 cases of aSAH secondary to ruptured blister aneurysms, reported that the treatment of ruptured blister aneurysm with Pipeline™ Embolization Device was a safe and durable option.[153] In a study of 8 patients, 5 of which had SAH secondary to ruptured blister aneurysm, Chalouhi et al. reported that given the limitations of other treatment modalities and the challenging

nature of blister aneurysm, flow diversion may be a valuable option for these lesions.[154] In a study of 55 aneurysms (11%, 6/55 had SAH) in 45 patients, Cinar et al. reported that Pipeline™ Embolization Device treatment achieved exclusion of the aneurysm and maintained a relatively high occlusion rate at 6 months.[155] Martin et al., in a study of 3 patients with ruptured intracranial aneurysms, suggested that the endovascular treatment with the Pipeline™ Embolization Device may be a viable treatment option for otherwise difficult to treat aneurysm morphologies in the context of acute SAH.[156]

Overall, published literature on the use the Pipeline™ Device for treatment of RIAs suggests that it is a feasible treatment option that was safe and effective, and/or led to good clinical outcomes.

3.4.2. Pipeline™ Shield for Treatment of Ruptured Aneurysms with Single Antiplatelet Therapy

One study[40] and 2 case reports[51,52] have been published on the treatment of ruptured aneurysms with the Pipeline™ Shield Device using only a single antiplatelet therapy.

Manning et al. evaluated the safety and efficacy of Pipeline™ Shield Device with single antiplatelet therapy (APT) for the acute treatment of 14 aSAH in 14 patients.[40] Aneurysm morphology was saccular in 50% (7/14), fusiform in 35.7% (5/14), and blister in 14.3% (2/14) of cases. The mean aneurysm size was 8.8 mm and aneurysms were mostly located in the anterior circulation (57.1%; 8/14). Pipeline™ Shield Device deployment was successful in all (100%) patients with a mean of 1.2 devices/patient. Adjunctive coil embolization was performed in 85.7% (12/14) of patients. Immediate aneurysm occlusion (Raymond-Roy 1) was achieved in 50% (7/14) of patients and almost total occlusion (Raymond-Roy 2) was achieved in 21.4% (3/14) patients. Incidents of intraoperative stent thrombosis, platelet aggregation, or hemorrhage, or any other operative complications were not identified immediately after treatment. On post-operative day 1, complete stent thrombosis was observed in 7.1% (1/14) of patients, who was treated successfully with endovascular thrombectomy. Minor non-flow-limiting platelet aggregation was reported in 14.3% (2/14) of patients at follow-up of 2 days. Mortality was reported in 21.4% (3/14) of patients before the acute hospital discharge, 1 patient died due to aneurysmal rebleeding and 2 patients died due to medical complications (hospital-acquired pneumonia). Mortality was associated with older patients (P = .029). Symptomatic and asymptomatic complications were observed in 21.4% (3/14) and 14.3% (2/14) of patients, respectively. The permanent treatment-related morbidity and mortality rates were 7.1% (1/14) and 7.1% (1/14) of patients, respectively. The use of a postoperative heparin infusion (n = 5) was associated with a higher rate of all complications (80.0% vs. 11.1%, P = .023) and symptomatic complications (60% vs. 0.0%, P = .028). Nine (64.3%) patients were functionally independent on discharge from the treatment center. The authors concluded that the Pipeline™ Shield Device might be safe to use for the treatment of acutely ruptured intracranial aneurysms with single APT.[40]

Hanel et al. presented a case report of Pipeline™ Shield Device in the treatment of a ruptured fusiform aneurysm using aspirin as antiplatelet monotherapy.[52] The patient was a 48-year-old man with Fisher grade III SAH and fusiform aneurysm in the right vertebral artery on presentation. He received Pipeline™

Shield Device treatment with aspirin monotherapy considering risks associated with dual APT in the setting of SAH. Cone-beam CT demonstrated good wall apposition of the Pipeline™ Shield Device within the intracranial segment. At 10 days postintervention, a follow-up angiogram revealed complete obliteration of intracranial segment of the right vertebral artery and evidence of good collaterals flow; however, thrombosis of the device was observed. Aspirin response test showed inadequate platelet reactivity. The patient was discharged at 16 days post-procedure with a mRS of 3. At 1-month follow-up, the patient was found with a mRS of 2. The authors concluded that, although the introduction of Shield Technology™ could potentially reduce thromboembolic complications, future well-controlled studies in ruptured and unruptured aneurysms were needed to guide the utilization of Pipeline™ Shield Device.[52]

Chiu et al. presented the first case of an acute flow diversion using only aspirin as sole oral antiplatelet agent.[51] The patient was described as a 48-year-old man with a World Federation of Neurological Surgeons grade 5 SAH, secondary to a ruptured intradural left vertebral artery dissecting aneurysm. The Pipeline™ Shield Device was deployed across the aneurysm, and 12 detachable coils were deployed in the jailed aneurysmal lumen, resulting in near stasis. On completion, 20 mg of abciximab were administered intravenously. The patient was on a 5-day heparin infusion and continued daily aspirin antiplatelet therapy. On week 1, a repeat angiogram demonstrated a Pipeline™ Shield Device construct with stasis in the perfused portion of the aneurysm sac. On week 2, follow-up magnetic resonance imaging (MRI) demonstrated no evidence of residual aneurysm and a single small left cerebellar hemispheric diffusion weighted imaging abnormality was noted. On week 6, MRI demonstrated no further infarcts were identified. On week 7, the patient was independent but in rehabilitation. The authors suggested that it may be reasonable to place the Pipeline™ Shield Device with only aspirin loading and full dose heparinization in acute cases.[51]

Overall, several studies/case reports on usage of the Pipeline™ Embolization Device[153,155-157] and recent reports with the use of Pipeline™ Shield Device[40,51,52] (with single antiplatelet agent) for treatment of ruptured and/or fusiform/dissecting aneurysms shows strong preliminary evidence supporting its safety and effectiveness in these complex aneurysms.

3.5. Purpose

The ELEVATE study is a prospective, multicenter, single-arm, adaptive IDE study of the Pipeline™ Shield Device for the treatment of adults (≥ 22 and ≤ 80 years of age) with acutely ruptured wide-neck (neck ≥4mm or dome to neck ratio ≤ 1.5) intradural aneurysms. The primary purpose of the ELEVATE study is to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone (**Study Rationale Section 5.2**). The primary safety and effectiveness of the Pipeline™ Shield Device will be assessed through incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up., and complete angiographic occlusion without significant stenosis (≤

50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure, respectively.

Secondary safety and effectiveness endpoints are detailed in **Section 4.1.2**.

4. Objectives and Endpoints

4.1. Objectives

The objective of the study is to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck (neck ≥4 mm or dome to neck ratio ≤1.5) intradural aneurysms not amenable to surgical clipping and coiling alone.

4.1.1. Primary Endpoints

Primary Safety Endpoint: Incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up.

- Major stroke is defined as a stroke which is present for ≥ 24 hours and increases the NIHSS of the subject by ≥ 4.

Primary Effectiveness Endpoint: Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure.

- Living subjects who do not present for 365-day follow up angiography will be treated as missing at follow-up and imputed using a multiple imputation procedure.
- Aneurysm occlusion according to the Raymond Roy Scale[127] and parent artery stenosis will be assessed by the imaging Core Lab (**Section 12.3**). Rebleeding and retreatment will be assessed by the Investigator.

4.1.2. Secondary Endpoints

1. Incidence of Pipeline™ Shield Device deployment success*
2. Incidence of target aneurysm rebleed through 180-day and 365-day follow-up post-procedure
3. Incidence of neurological hemorrhagic serious adverse events post-procedure through 180-day and through 365-day follow-up
4. Incidence of ipsilateral major stroke** or neurological death post-procedure after 30 days through 180-day and through 365-day follow-up
5. Incidence of any ipsilateral stroke post-procedure after 30 days through 180-day and through 365-day follow-up
6. Incidence of good clinical outcome (mRS 0-2) at 30-day, 180-day, and 365-day follow-up
7. Incidence of parent artery thrombosis through 365-day follow-up
8. Incidence of in-construct stenosis > 50% through 365-day follow-up
9. Incidence of target aneurysm retreatment through 180-day and through 365-day follow-up
10. Incidence of peri-/post-procedural serious adverse events related to the device, procedure or antiplatelet therapy through 180-day and through 365-day follow-up

11. Incidence of neurological death or major stroke** post-procedure through 180-day follow-up
12. Incidence of complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 180-day follow-up post-procedure

*Device deployment success is the successful implantation of the device at the target location.

**Major stroke: A stroke, which is present for ≥ 24 hours and increases the NIHSS of the subject by ≥ 4.

5. Study Design

This is a prospective, single-arm, multicenter, adaptive IDE study to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone.

Up to 200 subjects may be enrolled (consented) to attain a target sample size of 100 evaluable subjects who will undergo treatment with available data up to 365 days. The upper limit of up to 200 subjects to be enrolled (consented) accounts for a potential increase in the target number of evaluable subjects post-interim analysis and for a higher number of screen failures due to the emergent nature of this study in which subjects cannot be screened based on inclusion and exclusion criteria prior to arterial puncture and cannot be assessed by a Physician Screening Committee (PSC) until after consent. To avoid site-specific bias, the attempted procedure will be allowed for a maximum of 20% of the total number of evaluable subjects at each participating investigational site. Sponsor approval must be obtained prior to enrolling and treating additional subjects.

Up to 45 investigational sites may participate; inclusive of up to 40 investigational sites in the U.S. and up to 5 investigational sites outside U.S. (OUS).

Subject data will be collected at the time of enrollment (consent) through subsequent follow-up visits until conclusion of subject's study participation (e.g. completion of 365-day visit, subject/physician withdrawal, etc.).

5.1. Duration

Subjects with an attempted procedure to deploy Pipeline™ Shield Device are required to participate in the study for 365 days for the study endpoints and are expected to complete 30-day, 90-day, 180-day and 365-day follow-up visits. The overall study duration is approximately 5 years.

5.2. Rationale

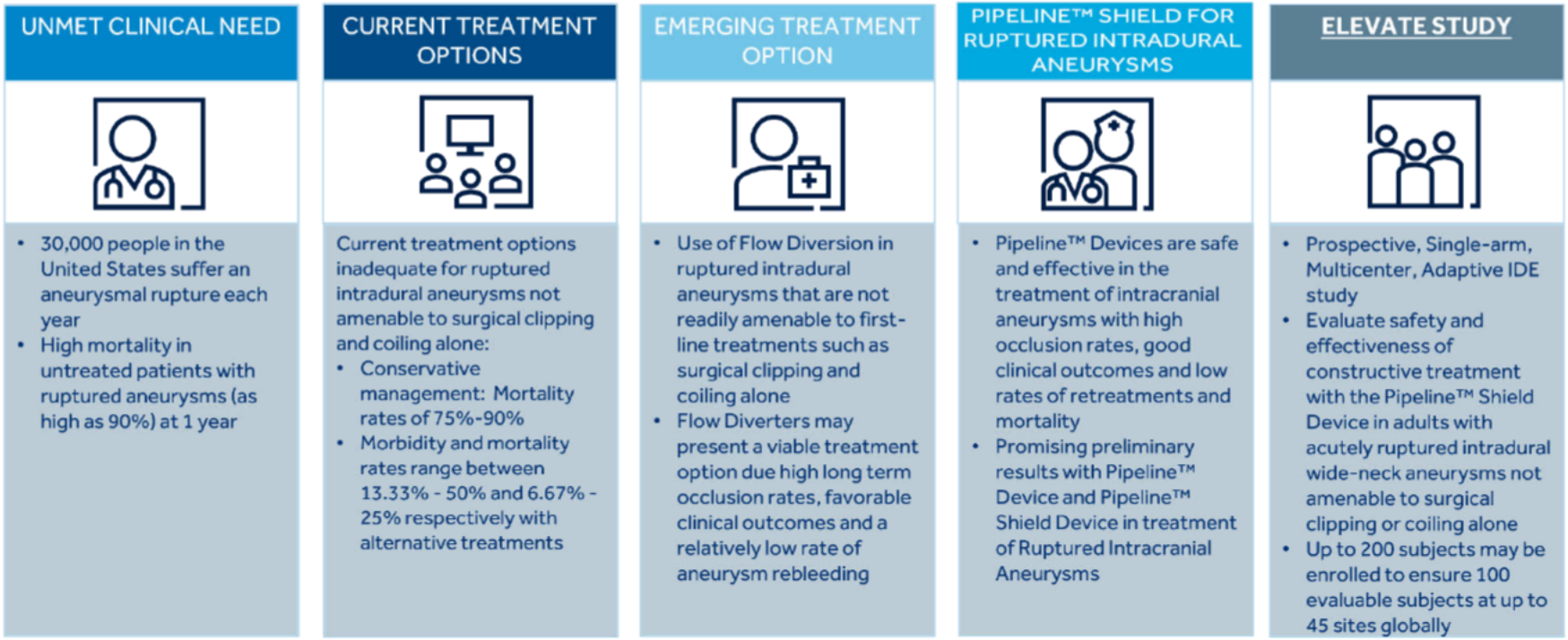


Figure 5-1. ELEVATE Study Rationale

Unmet Clinical Need

Ruptured intracranial aneurysms (RIAs) are amongst the most dangerous cerebrovascular lesions, characterized by acute presentation and dismal natural history if not correctly diagnosed and treated promptly.[9,10,54] Approximately, 3% of the population harbors an unruptured intracranial aneurysm,[1] and as many as 29% of unruptured intracranial aneurysms were reported to rupture during a lifelong follow-up.[2] An estimated 30,000 people in the United States suffer an aneurysmal rupture each year.[3] Aneurysmal SAH challenges the healthcare system as it is associated with a high case fatality rate (range between 32% and 67%[11]), occurs at a relatively young age compared with other types of stroke, and many survivors are left in a functionally dependent state.[4-6] Currently published literature suggests that patients with RIAs have poor outcomes with[6-8] current treatment options while others may not receive any treatment since current treatment options may be unsuitable based on aneurysm characteristics.[9,10]

Current Treatment Options

Current treatment options for patients with RIAs include conservative management, surgical clipping and endovascular treatment such as endovascular coiling. Additionally, various treatment modalities such as wrapping, bypass with parent artery trapping, microsurgical wrapping with autologous muscle and parent artery occlusion are currently followed for ruptured aneurysms unamenable to both, clipping and coiling.[17-20,60] Conservative management of RIAs unamenable to both, clipping and coiling, have poor outcomes; and mortality rate among hospital-admitted poor-grade patients with untreated RIAs at 1-year was reported as high as 90%.[9] During a lifelong follow-up of 510 untreated aSAH patients, the 1-year mortality rate was 65%, 5-year mortality 69%, and 10-year mortality 76%.[9] In the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage, approximately 2 out of 3 patients (378/568 patients) with aSAH died and 40% of these deaths had occurred within six months of hemorrhage.[10] Morbidity and mortality rates ranging between 13.33% - 50%[17-20] and 6.67% - 25%,[17-20] respectively, have been reported in patients with unclippable and uncoilable RIAs after alternative treatments such as wrapping, bypass with parent artery trapping, microsurgical wrapping with autologous muscle and parent artery occlusion.[17-20] Even in cases of ruptured aneurysms that were amenable to treatment such as surgical clipping and coiling, high mortality rates and poor outcomes have been reported.[6-8] Coil embolization of RIAs may be challenging based on aneurysm size and morphology as well as characteristics of the vessel wall.[13-16]

Emerging Treatment Option

Flow diversion therapy with Pipeline™ Devices offers a treatment of choice for patients with acutely ruptured wide-neck aneurysms for which standard techniques such as surgical clipping or coiling alone cannot be used.[25-29] Thus, endovascular reconstruction of the diseased segment with stents flow diverters has gained increasing acceptance[16,21,22] due to lower rate of recurrence[23] and procedure-related mortality.[24]

Authors of two meta-analysis[16,21] and AlMatter et al.[22] concluded (**Section 3.4**) that flow diversion may present a viable treatment option for ruptured intracranial aneurysms that are not readily amenable to first-line treatments such as coil embolization or surgical clipping,[21] or when traditional treatment methods are unfeasible.[16,22] Flow diverters have shown high long term occlusion rates,[16] favorable clinical outcomes[21] and a relatively low rate of aneurysm rebleeding[16] in treatment of RIAs. The "2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage"[158] recommends that for patients with aSAH from ruptured wide-neck aneurysms not amenable to surgical clipping or primary coiling, endovascular treatment with stent-assisted coiling or flow diverters is reasonable to reduce the risk of rebleed. Administration of antiplatelet medications to reduce the risk of thromboembolic complications in generally recommended when using flow diverters.[159,160]

Pipeline™ Shield Device for Ruptured Intradural Aneurysms

The Pipeline™ Embolization Device has been commercialized in the United States since 2011 for the endovascular treatment of adults with large (≥ 10-24 mm) or giant (≥ 25 mm) wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments. Over time, additional long-term data has been generated (**Section 3.3**) which further confirms the safety and effectiveness of the Pipeline™ Embolization Device for this indication. Pipeline™ Flex Device and Pipeline™ Shield Device were commercialized in the U.S. in 2015 and 2021, respectively. Based on the PREMIER study (**Section 3.3.1.5**), the Pipeline™ Flex Embolization Device is also indicated for use in the internal carotid artery up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysm arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm. Additionally, outside the United States, the Pipeline™ Embolization Device has been approved and commercialized since 2008 for endovascular embolization of cerebral aneurysms.

Even though the Pipeline™ Embolization Device and Pipeline™ Flex Device have been associated with high long-term complete aneurysm occlusion rates, low retreatment and no recurrence rates, one of the major concerns has been the associated risks such as ischemic complications, including the risk of thromboembolism and stenosis.[35-38] These risks may be due to the high surface area of metal coverage of Pipeline™ Embolization Device (metal coverage higher than that of self-expanding stents).[35-38]

Thromboembolic complications (e.g. thrombosis) can result due to surface activation (vascular endothelial/vessel wall injury), disruption of blood flow, or alterations in the constitution of the blood (hypercoagulability) based on the principles of Virchow's triad.[42] The Virchow's triad is applicable irrespective of vessel bed location. Of the three contributing factors for the thromboembolic complications, surface or contact activation is influenced by device material.[42] Flow diverters which are implanted intraluminal typically have high metal coverage (30-35%) may therefore contribute to material contact activation. Continued improvement of the Pipeline™ family of devices resulted in the

development of the third-iteration flow diverter, Pipeline™ Shield Device, to address surface activation due to device materials (material thrombogenicity).

Shield Technology™ utilizes a PC surface modification to the existing implant combined with the Pipeline™ Flex Device delivery system. The Shield Technology™ surface modification applied to the implant is a well-understood, inert, non-biodegradable, synthetic PC polymer material that is chemically bonded to the braid surface. The polymer is a chemically derived material, created to mimic the outer membrane of a human red blood cell. Shield Technology™ reduces the material thrombogenicity of the braid surface compared to the bare metal Pipeline™ Flex Device implant based on bench data with human platelets and plasma.[43-50] AlMatter et al. opined that the surface modification (Shield Technology™) to reduce the inherent thrombogenicity of flow diverters is a promising recent advancement.[22]

The initial hypothesis of the ELEVATE IDE suggested that only patients with ruptured shallow intradural aneurysms not amenable to both, coiling and clipping may benefit from treatment with flow diversion since they have no other treatment options. However, emerging data shows that flow diversion treatment in ruptured wide-neck aneurysms may be beneficial, with or without coiling,[16,21,22] when these aneurysms are not amenable to surgical clipping and coiling alone. The "2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage",[158] which represents a thorough review of this therapeutic space, recommends that for patients with aSAH from ruptured wide-neck aneurysms not amenable to surgical clipping or primary coiling, endovascular treatment with stent-assisted coiling or flow diverters is reasonable to reduce the risk of rebleed. Therefore, based on the updated Guideline and recent evidence, the indication under investigation has been expanded to include ruptured intradural aneurysms that are wide-neck (neck $\geqslant$4mm or dome to neck ratio $\leqslant$1.5) and not amenable to surgical clipping and coiling alone; such aneurysms may be treated with the Pipeline™ Shield Device (with or without coiling) at the index procedure within the ELEVATE IDE.

ELEVATE STUDY

The ELEVATE study is designed as a prospective, single-arm, multicenter, adaptive IDE study to assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone. The primary safety and effectiveness endpoints of the ELEVATE study are the incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up, and complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure, respectively. The primary endpoints have pre-defined thresholds for evaluating primary safety and effectiveness endpoints based on relevant published literature.

The proposed study design is a single-arm study. As with the evaluation of the Pipeline™ Embolization Device in the PUFs[120] and PREMIER[161] IDE studies, a randomized controlled study is not feasible for the

evaluation of the Pipeline™ Shield Device due to the lack of an appropriate control or specific device with regulatory clearance to treat acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone.

6. Product Description

6.1. General

The study device under investigation is the Pipeline™ Shield Device.

Figure 6-1. Pipeline™ Shield Device Braided Implant



Figure 6-2. Pipeline™ Shield Device Delivery System

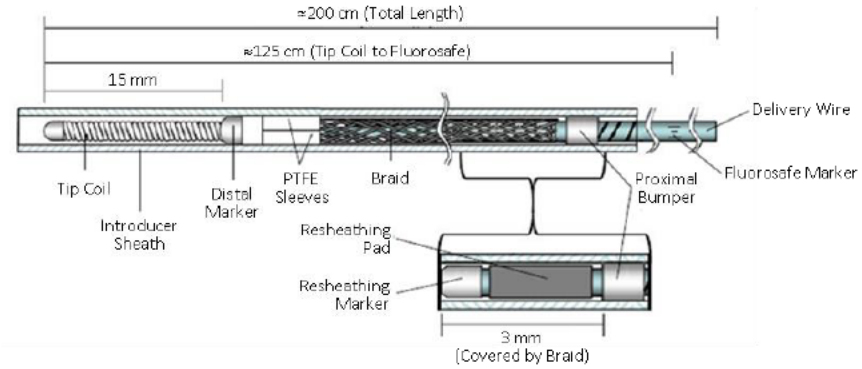


Diagram of the distal end of the Pipeline™ Shield Device delivery system loaded into the introducer sheath.

The Pipeline™ Shield Device (P100018/S026) is similar to the FDA approved Pipeline™ Flex Device (P100018/S011).

6.1.1. Implant Description

The Pipeline™ Shield Device consists of a permanent implant combined with a guidewire-based delivery system. The Pipeline™ Shield Device implant is a braided, multi-alloy, mesh cylinder woven from platinum/tungsten and cobalt- chromium-nickel alloy wires. An image of the Pipeline™ Shield Device braided implant is shown in **Figure 6-1**. The woven wires of the device provide approximately 30% metal coverage of the arterial wall surface area. The braided implant is designed for placement in a parent vessel across the neck of an intracranial aneurysm. The expanded or un-constrained diameter is designed to be 0.25 mm larger than the labeled diameter. The implantable portion of Pipeline™ Shield Device (braided implant) remains identical to the current Pipeline™ Flex braided implant with the exception of the surface modification material (synthetic PC polymer) and the manufacturing steps associated to apply the surface

modification. [redacted]

6.1.2. Delivery System Description

The Pipeline™ Shield Device (P100018/S026) (Canada MDL: 102166) delivery system (**Figure 6-2**) is identical to the Pipeline™ Flex Device delivery system (P100018/S011) (Canada MDL: 82882). There are no changes to the Pipeline™ Flex Device delivery system for Pipeline™ Shield Device. The description of the device delivery system is provided below for reference.

The Pipeline™ Shield Device braided implant is mounted on a 304 stainless steel micro guidewire 200 cm long and compressed inside an introducer sheath. The Pipeline™ Shield Device braided implant is designed to be delivered through a compatible microcatheter of 0.027 inch (0.69 mm) inside diameter at least 135 cm in length.

The tip coil is made of platinum-tungsten alloy, the proximal bumper is platinum-iridium alloy, and the tip, distal and proximal solder joints are composed of tin-silver. The protective sleeves are designed to protect the distal portion of the braided implant while the Pipeline™ Shield Device is advanced through the microcatheter. The protective sleeves are made of polytetrafluoroethylene (PTFE), a flexible fluorocarbon material able to withstand multiple resheathing cycles.

The proximal bumper and resheathing pad allow the user to push the Pipeline™ Shield Device braided implant out of the microcatheter when the delivery system is advanced. The resheathing pad also allows the user to resheath the braided implant back into the microcatheter, up to two times. The resheathing marker provides the user fluoroscopic visualization for the limit of resheathing the Pipeline™ Shield Device braided implant.

6.1.3. Shield Technology™

The Pipeline™ Shield Device implant is treated with an inert surface modification (Shield Technology™) process. This is the same surface modification, applied via the same manufacturing (submerge) process, and composed of the same materials as approved under PMA P100018/S026. The Shield Technology™ surface modification adds a well-understood, inert, non-biodegradable, synthetic PC polymer that is covalently bonded to the surface of the braided implant. The result is a layer only 3 nanometers in thickness on the surface of the braid wire. In addition, the 3-nanometer thick layer is significantly smaller than 10 microns (10,000 nanometers), which is the smallest collection size for particulate matter in injections per USP <788>. The surface modification is primarily composed of a PC polymer (Lipidure®-NH01). The implant is also pretreated with (3-Glycidyloxypropyl) trimethoxysilane, which acts a coupling agent to covalently bond the PC polymer to the implant. PC is an electrically neutral component of the outer membrane of red blood cells. Because PC is abundant on the surface of red blood cells, surface

modification of a device with PC physiologically mimics the cell membrane. In vitro assessments of PC surface modified devices have demonstrated reduced material thrombogenicity.[43-50]

6.2. Manufacturer

The manufacturer of the Pipeline™ Shield Device is Micro Therapeutics, Inc. d/b/a ev3 Neurovascular. Micro Therapeutics, Inc. d/b/a ev3 Neurovascular is a wholly owned subsidiary of Medtronic.

6.3. Biocompatibility Summary

All biocompatibility tests for the Pipeline™ Shield Device were completed and all test results passed the acceptance criteria (per ISO 10993-1:2009, FDA G95-1, and FDA Draft Guidance: Use of International Standard ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" dated April 23, 2013).

6.4. Product Labeling and Indication for Use

Pipeline™ Shield Device is an approved, commercially available device, but is not approved for the indication under investigation and therefore must be used per the Clinical Investigation Plan (CIP) and as specified in the country-specific investigational IFU (M009043CDOC2 (U.S.) and M031954DOC2 (Canada)).

Per the investigational IFUs, the Pipeline™ Flex Embolization Device with Shield Technology™ is indicated for the endovascular treatment of adults (22 years of age or older) with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone.

6.5. Product Training Requirements

Pipeline™ Shield Device must only be used by implanting investigator trained in percutaneous neurointerventional techniques and procedures at medical facilities with the appropriate fluoroscopic equipment. Fellows are not permitted to implant Pipeline™ Shield Device or any other adjunctive device for the treatment of aneurysms during the study procedure. Prior to implantation of the Pipeline™ Shield Device, implanting Investigator(s) will be trained on, at a minimum, device usage, Clinical Investigation Plan (CIP) and the investigational IFU.

6.6. Product Accountability

6.6.1. U.S. Product Accountability

Model identifiers and lot numbers of all Pipeline™ Shield Devices that are opened during the procedure for enrolled subjects will be recorded. Due to commercial availability, device shipments and returns will not be tracked for this study.

6.6.2. Canada Product Accountability

All investigational devices will be tracked and recorded by model identifier and lot number. All devices must be kept in a secured location with limited access. Complete accountability for each device must be maintained, including shipping, receiving and final device disposition. All unused devices must be returned to the Sponsor at the conclusion of the study or upon product expiration. The Sponsor will perform periodic reconciliation of the investigational product to ensure traceability.

7. Study Site Requirements

7.1. Investigation Site Selection

Investigational sites will be selected based upon a site qualification assessment, appropriate facilities, and the qualifications of the Investigator. The Sponsor will assess each potential investigational site and evaluate Investigator and the site study personnel's experience with the intended procedures and ability to conduct the study according to the Clinical Investigation Plan.

To participate, the Investigator and investigational site should meet the following minimum criteria:

- Qualified by training, education and has relevant experience appropriate to the use of the Pipeline™ devices for the treatment of intracranial aneurysms
- Experience with clinical research and is expected to have adequate time and resources to conduct the study in accordance to Clinical Investigation Plan throughout the duration of the study
- Access to an adequate number of eligible subjects
- Ability to comply with applicable Institutional Review Board and regulatory requirements
- Investigators are not debarred, disqualified, or working under sanctions in the applicable regions
- Site has adequate facilities to conduct the study
- Principal Investigator is willing to assume full responsibility for performance of the research study in accordance with the Clinical Trial Agreement, Investigator Statement, Clinical Investigation Plan, Good Clinical Practice, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IRB/EC
- Willingness to provide direct access to original subject medical records, including electronic medical records, certified copies of subject medical records or over-the-shoulder access to subject medical records

Sponsor will maintain a list of investigational sites, names of the Principal Investigator responsible for conducting the study, and the associated IRB/EC.

7.2. Study Site Activation

During the site activation process, prior to subject enrollment, the Sponsor study team will ensure all necessary activities have occurred including, but not limited to:

- Completion of Site Initiation Visit
- IRB/EC approval of the current version of the CIP, ICF and other study documents as applicable (e.g., Instruction for Use)
- Execution of Clinical Trial Agreement

- Documentation of delegated tasks
- Training of site study personnel
- Collection of essential documents

The Sponsor study team will provide each investigational site with documentation of site/investigator readiness; this letter must be received prior to performing study related activities.

7.3. Site Study Personnel Training

Investigators and the site study personnel will be trained in accordance to their delegated task(s) as documented on the Delegation of Authority (DoA) Log prior to performing study-related activities and procedures and all training must be documented. Treating investigators will complete the product training requirements per **Section 6.5**. Existing site study personnel who have been delegated new tasks must complete required training prior to performing those activities.

8. Selection of Subjects

8.1. Study Population

The study population will consist of adults (22 – 80 years of age) with intradural acutely ruptured wide-neck (neck ≥4 mm or dome to neck ratio ≤ 1.5) aneurysms not amenable to surgical clipping and coiling alone.

8.2. Inclusion Criteria

Subjects for this study must meet ALL of the following criteria:

Imaging Criteria assessed by Physician Screening Committee:

1. Subject has a previously untreated, wide neck (neck ≥4 mm or dome to neck ratio ≤1.5), intradural, side-wall target aneurysm including a blister, fusiform, saccular or dissecting aneurysm that is not amenable to surgical clipping and coiling alone, as confirmed on conventional digital subtraction angiography (DSA).
2. Subject has a target ruptured intracranial aneurysm with a proximal and distal vessel diameter suitable for treatment using available device sizes of the Pipeline™ Shield Device.

Clinical Criteria:

3. Subject is ≥ 22 and ≤ 80 years of age at time of consent.
4. Subject has an acutely ruptured aneurysm (within the last 30 days prior to the planned index procedure) with Hunt and Hess Scale 1, 2 or 3.
5. Subject or subject's Legally Authorized Representative (LAR) has provided written informed consent using the IRB/EC approved Informed Consent Form and agrees to comply with Clinical Investigation Plan requirements. HIPAA/data protection authorization has been provided and signed by the subject or subject's LAR.

8.3. Exclusion Criteria

Subjects shall be excluded from the study if ANY of the following conditions exist:

Imaging Criteria assessed by Physician Screening Committee:

1. Subject's vessel characteristics (e.g. severe vasospasm, tortuosity, stenosis, morphology) precludes safe endovascular access to the aneurysm to treat with the Pipeline™ Shield Device.
2. Subject has aneurysm vessel characteristics (e.g., parent vessel stenosis, irregular morphology) that would preclude the device from fully conforming to the parent vessel to reduce any risk of embolic complications, retreatment, or device movement.

3. Subject has true bifurcation aneurysm or aneurysm with vessels that cannot be separated from the fundus with the placement of the Pipeline™ Shield Device.

Clinical Criteria:

4. Subject with intraparenchymal hemorrhage.
5. Subject is unable to undergo Nasogastric tube/Orogastric tube placement prior to device placement.
6. Subject has a pre-morbid mRS > 2.
7. Subject requires treatment of another aneurysm with another treatment modality within the affected territory of the target aneurysm during the study period.
8. Subject has a target ruptured aneurysm that is thought to be mycotic, including those caused by left atrial myxoma, or subject has an active systemic bacterial infection.
9. Subject with a requirement for continuous anti-coagulation.
10. Subject has a malignant brain tumor or vascular malformation (e.g. arteriovenous malformation).
11. Subject's target ruptured aneurysm has not been confidently determined by the treating physician to be the source of SAH.
12. Subject with known allergy to platinum or cobalt chromium alloy (including the major elements platinum, cobalt, chromium, nickel or molybdenum).
13. Subject has a known hypersensitivity to ticagrelor or aspirin.
14. Subject is unable to undergo DSA or DSA is determined unsuitable by the treating physician.
15. Subject has a serious or life-threatening comorbidity that could confound study results.
16. Subject is at high risk of noncompliance per treating physician due to reasons including but not limited to a history of substance abuse.
17. Subject is unable to complete scheduled follow-up assessments due to comorbidities, geographical limitations, or a life expectancy of less than 24 months.
18. Female subject, of child-bearing potential, who is pregnant (confirmed with a positive pregnancy test) or breastfeeding at the time of admission or plans to become pregnant during their participation in the study.
19. Subject is participating in another clinical trial at any time during the duration of the study that could confound the treatment or outcomes of this investigation.
20. Presumed septic embolus, or suspicion of microbial superinfection.

21. Subject with a known active COVID-19 viral infection.
22. Subject in whom a pre-existing stent is in place in the parent artery at the target aneurysm location.

8.4. Subject Enrollment

During the baseline screening visit, subject will be screened for enrollment eligibility in accordance to **Sections 9.4** and **9.5**. A subject is considered enrolled when the informed consent has been signed by the subject (or subject's legally authorized representative (LAR)).

Subjects who sign the informed consent but is determined as ineligible prior to the index procedure and device implant will be considered a screen failure. A screen failure subject can be classified as:

- Pre-screen Failure: A subject who did not meet eligibility and consent was not signed.
- Screen Failure: An enrolled subject who was determined to be ineligible for the study prior to the arterial puncture on the day of the index procedure.
- Procedural Screen Failure: An enrolled subject who was determined to be ineligible after arterial puncture per the pre-procedural DSA imaging on the day of the index procedure prior to device implant.

Screen Failure subjects should be exited from the study and no further follow-up is required in these subjects.

9. Study Procedures

9.1. Schedule of Events

An overview of the assessments to be performed at each follow-up interval, along with the required window, is provided in **Table 9-1**. Scheduled visits occurring outside of the specified window will be considered a protocol deviation. An overview of the study procedures is shown in **Figure 9-1**.

Table 9-1. Visit and Assessment Schedule

	Baseline[1] Screening	Index Procedure		Post Procedure		Follow-up[12]				
		Pre-implant	Post-Implant	24-hour	Prior to discharge	30-day[15]	90-day	180-day	365-day	Un-scheduled
	-	*Day 0*	*Day 0*	*± 12 hours*	-	*± 14 days*	*± 28 days*	*± 28 days*	*± 56 days*	-
CT or MRI	◆[7]			◆	◆[11]	◆[11]	◆[11]	◆[11]	◆[11]	◆[11]
Inclusion/ Exclusion	◆									
Demographics	◆									
Medical/Surgical History	◆									
COVID-19 testing	◆[10]				◆[10]	◆[10]	◆[10]	◆[10]	◆[10]	◆[10]
Concomitant Medications	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Pregnancy Test	◆[3]									
Hunt and Hess Scale	◆									
Modified Rankin Scale (mRS)	◆[4]				◆[19,5]	◆[5]	◆[5]	◆[5]	◆[5]	◆[13]
NIH Stroke Scale (NIHSS)	◆			◆[6]		◆[6]	◆[6]	◆[6]	◆[6]	◆[13]
Clinical Vignette					◆[18]			◆[18]		
Informed Consent	◆									
CIP Specified Medication			◆	◆	◆	◆	◆	◆[17]		
Glasgow Coma Scale	◆			◆						
Digital subtraction angiography (DSA)		◆[8]	◆		◆	◆[11]	◆[11]	◆	◆	◆[11]
Adverse Event		◆[9]	◆	◆[14]	◆[14]	◆[14]	◆[14]	◆[14]	◆[14]	◆[14]
Laboratory tests[2]		◆			◆					
Fisher Grading Scale	◆									
ARU/PRU test(s)				◆[16]						

[1] Screening assessments and baseline visit may be conducted on Day 0 prior to the procedure.

[2] Laboratory tests include CBC, CHEM-7, and coagulation profile. Prior to discharge, if multiple lab values are available, the one closest to discharge must be recorded in eCRFs.

[3] Pregnancy test (serum or urine) is only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test.

[4] Premorbid modified Rankin Scale is completed any time prior to procedure by obtaining verification from an individual aware of the subject's functional status prior to SAH (e.g., family member, friend, etc.).

[5] mRS to be carried out by a certified independent assessor. mRS assessment at 90 days post-stroke must also be performed by a certified independent assessor.

[6] NIHSS to be carried out by a delegated qualified site study personnel.

[7] CT imaging is required to confirm SAH at baseline screening.

[8] Pre-procedure DSA image must be sent to the PSC for review; approval by PSC is needed in order for subject to be treated with the Pipeline™ Shield Device.

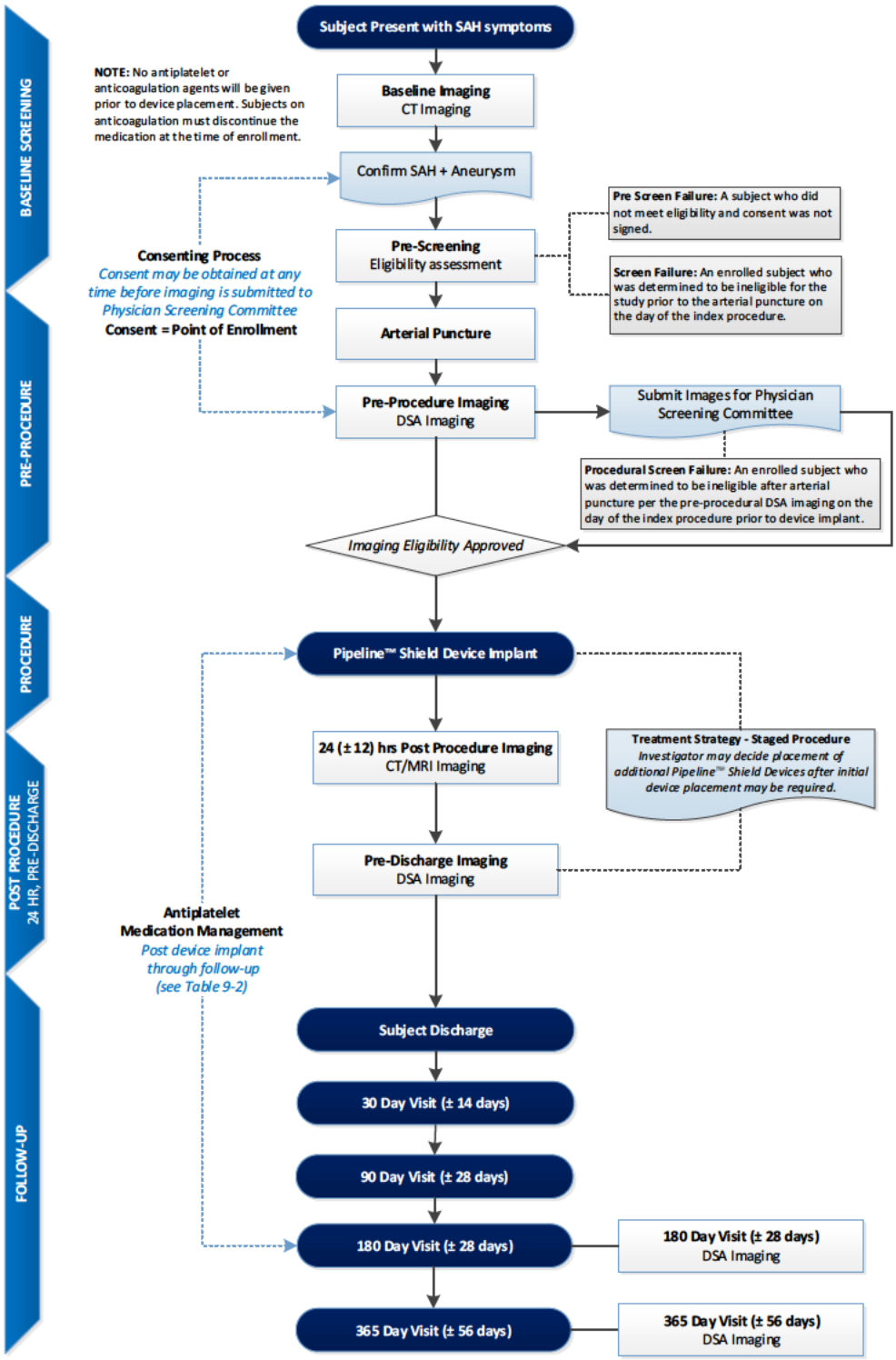
[9] Collection of adverse events will start from the point of arterial puncture. Screen Failure subjects and Procedural Screen Failure subjects will be followed for safety until subject is exited from the study. Subjects with an unsuccessful implant procedure will be followed for safety at 180-day post-procedure.

[10] If performed per SOC, collect data for COVID-19 testing.

[11] To be collected if conducted per standard of care (SOC). Any images taken per SOC should be sent to the Core Lab.

[12] Follow up schedule will be based on Time 0, which is the day of the last device implant during index hospitalization (i.e., when staged procedure is performed). If no staged procedure occurred, then Time 0 will equal Day 0.
[13] NIHSS and mRS assessments will be required only for those subjects with any presumed events of neurological nature. If mRS assessment is carried out at an unscheduled visit 90 days post-stroke, the assessment should be carried out by a certified independent assessor.
[14] For stroke events, NIHSS will be performed at the time of event, at 24 hours and at discharge; mRS must be completed a minimum of 90 days post-stroke event.
[15] If the subject is still in the hospital at the start of the 30-day visit window then the 30-day visit should be completed while the subject is in the hospital.
[16] Aspirin Reaction Units (ARU) test will be done at 24 - 48 hours post-procedure in each subject (after at least one dose of aspirin has been given and after the effects of Glycoprotein IIb/IIIa medication, eptifibatide or tirofiban, have dissipated based on the drug half-life). Subject(s) with ARU ≥ 550 units will be considered "non-responder(s)" to aspirin. For subjects who are non-responders to aspirin, P2Y12 Reaction Units (PRU) test will be performed within 24 hours of the ARU test (after at least one dose of ticagrelor). PRU levels within therapeutic range of ≥ 60 and ≤ 200 are acceptable. If subject's PRU levels are within the therapeutic range, subject will be given ticagrelor (90 mg BID) for a minimum of 6 months. If PRU levels are outside the therapeutic range, the investigator will appropriately switch the maintenance dose of antiplatelet medication to clopidogrel (Plavix) 75 mg QD or prasugrel (Effient) 10 mg QD for a minimum of 6 months after confirming the subject's responsiveness to either of these anti-platelet agents by repeated PRU tests, as needed. Note that prior to carrying out the PRU test and starting the maintenance dose, subjects should be administrated a loading dose of clopidogrel (600 mg) or prasugrel (60 mg).
[17] Subject is required to take CIP specified medication for a minimum of 180 days.
[18] If independent mRS assessor scores the mRS as ≥3, the investigator or physician involved in the management and care of the subject shall assess and document the subject's cause of disability. If applicable, the 180-day clinical vignette will be completed at the 90-day post-stroke unscheduled visit.
[19] mRS to be collected at discharge.

Figure 9-1. Study Overview



9.2. Data Collection

Data collection requirements are summarized in **Table 9-1** and throughout **Section 9**.

9.3. Scheduled Follow-up Visit Windows

Follow-up visit windows are summarized in **Table 9-1**.

9.4. Subject Screening

Subjects should be clinically evaluated in the same manner as any routine acute subarachnoid hemorrhage patient. Upon admission to the treating hospital, subjects will be pre-screened to determine their initial eligibility and interest in the study. Initial evaluation of the inclusion/exclusion criteria will be completed during the baseline screening visit and any tests/procedures that are routinely performed as standard of care can be completed without obtaining informed consent.

All subjects that are considered for the study should be included on the study pre-screening log with the reason for non-eligibility, as determined by the Investigator. The screening log serves as a method for the Sponsor to assess selection bias in the study.

9.5. Subject Consent

Informed consent is defined as legally effective, documented confirmation of a subject's, or subject's Legally Authorized Representative, voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. Legally Authorized Representative (LAR) refers to an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102 (c)) (21 CFR 50.3 (1)). Institutional or IRB/EC policies may also provide considerations and guidance for use of LAR in the research.

All informed consent documents used under this Clinical Investigation Plan including a Health Insurance Portability and Accountability Act (HIPAA)/data protection authorization consent, will be consistent with applicable elements of 21 CFR Part 50 and will be approved by the investigational site's reviewing IRB/EC prior to subject enrollment.

The informed consent form (ICF) will include, at minimum, the following:

- Purpose of the study
- Alternative treatments
- Procedures of the study including the need to return for 30-day, 90-day, 180-day and 365-day follow-up visits

- Participation is voluntary, and there is no penalty for withdrawal
- Potential risks and benefits of participation
- Compensation and expenses to subject, as applicable
- Contact information to ask questions or voice concerns

Prior to subject enrollment in the study, it is the responsibility of the delegated Investigator and/or site study personnel to conduct the consent process to provide each subject or subject's LAR full and adequate verbal explanation and written information of the ICF elements listed above. The subject or subject's LAR will be given ample opportunity to ask questions and to consider their decision.

Subject or subject's LAR must sign and date the IRB/EC approved ICF and the HIPAA/data protection authorization prior to participation in the study and prior the site study personnel conducting any study-specific evaluations and recording subject-related health information in the study database. Any tests/procedures that are routinely performed per standard of care may be completed without obtaining subject informed consent as part of the pre-screening assessment.

A copy of the ICF and HIPAA/data protection authorization will be given to the subject or subject's LAR, and another copy will be placed in the subject's medical record. The process of obtaining informed consent must also be documented in the subject's medical records.

Whenever new and significant information becomes available that may result in revisions to the ICF, the consented subject will be informed and may be asked to re-consent to continue participation in the study, as required by the IRB/EC. Any such revisions or updates to the ICF must be approved by the reviewing IRB/EC prior to consenting or re-consenting subjects.

9.6. Baseline assessment

Baseline screening assessments can also be conducted on the day of the scheduled device implant procedure. The following baseline assessments shall be performed and recorded in the eCRF:

- Inclusion/exclusion criteria
- Informed consent
- Demographics: age, gender, ethnicity and race
- Medical and surgical history
- COVID-19 test, if performed per standard of care (subjects that test positive are ineligible for the study)
- Pre-morbid modified Rankin scale (mRS) assessment
- National Institute of Health Stroke Scale (NIHSS) assessment
- Hunt and Hess Scale assessment
- Glasgow Coma Scale (GCS) assessment

- Fisher Grading Scale assessment
- Review of concomitant medications
- Computed Tomography (CT) imaging
- Pregnancy test for women of child-bearing potential

9.6.1. Baseline Screening Imaging

Baseline screening CT imaging is required to confirm subarachnoid hemorrhage.

9.6.2. Medical History

Medical history, surgical history and aneurysm specific history will be recorded for all subjects at the time of enrollment and will include those conditions that are observed or self-reported by the subject at the baseline visit.

Detailed symptoms and signs presented at baseline shall be recorded as medical history. Any worsening of these symptoms from the point of arterial puncture shall be recorded as adverse events in accordance with **Section 11**.

9.7. Prior and Concomitant Medications

Subjects on anti-coagulation must discontinue the medication at the time of enrollment. If the subject has an absolute requirement to be on anti-coagulation, then the subject is considered ineligible for the study.

Concomitant medications are to be collected starting at baseline and through the duration of the study which includes:

- All medications the subject is on at the time of enrollment
- Medications received on and following the index procedure day (Day 0) – further details in **Section 9.10** and **Table 9-2**
- Any new medications taken for intervention of study reportable events of interest

Change in previously recorded concomitant medications after the index procedure (Day 0) through study exit.

9.8. Pre-Procedure (Pre-Implant)

On the day of the procedure and prior to the device implant, the following assessments shall be performed and recorded in the eCRF:

- Catheter-based angiography (DSA imaging)
- Target aneurysm location and dimensions
- Review of concomitant medication

- Review of any adverse events (note: collection of adverse events begins from the point of arterial puncture)
- Laboratory tests (CBC, CHEM-7, and coagulation profile)

Imaging-based eligibility will be determined by the PSC based on the pre-procedure catheter-based angiography prior to device implant.

Prior to device implant and following induction of anesthesia, a nasogastric (NG) tube or orogastric (OG) tube will be inserted. If NG or OG tube cannot be inserted, then subject will be ineligible for the study.

9.8.1. Pre-Procedural Medication

No study-specific antiplatelet or anticoagulation agents will be given prior to the procedure (Day 0). Subjects on anticoagulation must discontinue the medication at the time of enrollment.

9.8.2. Pre-Procedural Imaging

Arterial access will be obtained per institutional standard of care and a sheath will be placed to accommodate either a diagnostic catheter, guiding catheter or guiding sheath based on the treatment plan. Conventional catheter based DSA imaging will be performed to include selective angiography from a catheter positioned within the cervical artery which supplies the vascular distribution of the target aneurysm.

The Investigator will submit these de-identified images, with measurements for the target aneurysm and parent vessel (diameter and length), to the PSC for their eligibility assessment and determination based on the imaging inclusion/exclusion criteria.

The following images shall be performed prior to implantation:

- 3-D DSA imaging pre-procedure to be used for final aneurysm measurements (if available)
- Two planes showing the entire vascular territory (either complete hemisphere or full posterior circulation filmed in the early venous phase)
- Views in the working projection with and without subtraction

9.9. Procedure

The study index procedure should take place immediately after all required clinical and imaging baseline assessments have been completed, informed consent have been obtained and the PSC confirms eligibility based on imaging criteria and procedural compatibility. Eligible subjects will be treated with the Pipeline™ Shield Device per the country-specific investigational IFU.

The following procedure data shall be collected and recorded in the eCRF:

- Procedure date
- Name of Primary interventionalist (implanting Investigator)
- Type and time of puncture
- Study device placement and resheathing information
- Device implant success
- Subject's radiation exposure (dose and fluoroscopy time)*
- Volume of contrast used
- Post-Pipeline™ Shield Device implant aneurysm occlusion, device placement and aneurysm status
- Procedural complications
- Record CIP specified antiplatelet/anticoagulation medications
- Concomitant medications
- Device details of Pipeline™ Shield Device
- If multiple Pipeline™ Shield Devices are implanted: reason for multiple device usage and total number of devices

*Note: Investigator and site study personnel should take all necessary precautions to limit X-ray radiation doses to subjects and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

9.9.1. Index Procedure (Day 0)

Step 1 - Endovascular Treatment: A therapeutic catheter access platform will be introduced into the targeted artery for the intervention. A microcatheter in accordance with Pipeline™ Shield Device country-specific investigational IFU, depending on the size of the Pipeline™ Shield Device, will be introduced and manipulated over a micro guidewire beyond the target aneurysm. The microwire will be removed. Super selective angiography and guiding catheter system control angiography will be performed at the discretion of the operator. Following measurements to guide device selection, a Pipeline™ Shield Device will be introduced into the microcatheter.

Step 2 - Pipeline™ Shield Device deployment: The Pipeline™ Shield Device will be deployed across the aneurysmal segment and control angiography will be performed. Immediately post implant, a half loading dose of Glycoprotein IIb/IIIa inhibitor, eptifibatide (Integrilin) or tirofiban (Aggrastat), will be administered.

Step 3 - Final Angiography: Immediate post-treatment angiograms in the AP, lateral, and working positions will be obtained. The following images shall be collected at the end of the procedure after implantation:

- 3-D DSA imaging (if available)

- Two planes showing the entire vascular territory (either complete hemisphere or full posterior circulation filmed in the early venous phase)
- Views in the working projection with and without subtraction

Step 4 - Treatment Completion: The catheters will be removed. Hemostasis will be achieved at the puncture site in accordance with institutional practice standards.

9.9.2. Procedural Imaging

De-identified DICOM images will be submitted to the Core Lab. The Investigator will take necessary steps to ensure that pre- and post- placement angiograms are performed using similar views, magnifications, and contrast amount so as to ensure valid "before-after" comparisons. Any complicating factors, such as vessel dissection or perforation, should be recorded as an AE. All pre-procedure, post-procedure and follow up angiograms shall be sent to a Core Lab to make a final determination of in-construct stenosis, parent artery thrombosis and aneurysm occlusion.

9.9.3. Usage of Multiple Pipeline™ Shield Devices

A maximum of 3 Pipeline™ Shield devices may be stacked at the target aneurysm's neck in order to increase the desired coverage density. Multiple devices can be utilized in order to build a construct (telescoping) to provide appropriate coverage, at any point within the treated artery.

9.9.4. Usage of Ancillary Devices

Ancillary devices that may be required for the study procedure include, but are not limited to, access devices, balloon guide catheters, intermediate support catheters, guidewires and microcatheters. Access devices, intermediate support catheters, and guidewires may be selected for use from FDA cleared devices as per Investigator preference and standard of care. When using a catheter labeled for femoral artery access exclusively or with access site unspecified, radial artery access should be used only when femoral artery access is not feasible. All endovascular devices are to be used in accordance with directions for use in the package insert approved by the FDA.

9.9.5. Usage of Adjunctive Devices

Adjunctive devices are defined as devices (other than the Pipeline™ Shield Device) that are used to treat the target aneurysm.

Adjunctive devices (e.g. coils) may be used during the index procedure in conjunction with the Pipeline™ Shield Device in order to protect the dome of the aneurysm and reduce the risk of re-rupture. The use of coils is not required and will be at the discretion of the treating physician.

9.9.6. No Treatment of an Eligible Subject with the Pipeline™ Shield Device (Unsuccessful Implant Procedure)

In the event a subject was consented, confirmed eligible per the PSC criteria and the implant procedure was attempted but not successful (i.e. successful introduction of the Pipeline™ Shield Device into the microcatheter but access to the aneurysm was not achieved or the Pipeline™ Shield Device was not deployed):

- Subject will remain in the study and will be exited after the 180-day follow up due to unsuccessful implant procedure, unless the subject exits the study prior to the visit (e.g., withdraws consent).
- Subject with an unsuccessful implant procedure is not required to return for the 30-day and 90-day visit and will be assessed at the 180-day follow-up visit.
- Any alternative treatments, if received, will be recorded.
- Subject will not be included in the per-protocol population.

9.10. Medical Management Pre and Post Device Implant

Medications administered during and after the Pipeline™ Shield Device implant procedure are detailed below and in **Table 9-2**.

9.10.1. Intra-Procedural Medication

General Anesthesia Medication: The subject will undergo the index study treatment procedure under general anesthesia. Medications appropriate for general anesthesia will be administered using standard hospital practice.

Medication during Procedure: Intra-procedural medications specific to the endovascular study procedure (e.g., anti-hypertensives, prophylactic antibiotics) must be recorded on the Con Meds eCRF. Administration of medications will be allowed as per clinical standard for the treatment of or prophylaxis of vasospasm encountered in the access to the intracranial vessels. The use of heparinized saline for drips and flush is allowed but a bolus of heparin should not be administered in any subject at the start of or at any time during the procedure.

Anesthetics and other standard of care medications for endovascular or surgical intervention (e.g., saline, povidone-iodine antiseptic, etc.) do not need to be collected in the eCRFs.

9.10.2. Post-Implant Medication

- Glycoprotein IIb/IIIa inhibitor: Immediately after Pipeline™ Shield Device implant, a half loading dose of Glycoprotein IIb/IIIa inhibitor, eptifibatide (Integrilin) or tirofiban (Aggrastat), will be given

to prevent intra-procedural thrombus formation. Administered dosage will be rounded down to the nearest whole milligram from calculated weight-based dosage.

- Eptifibatide (Integrilin): 90 µg per Kg,

or

- Tirofiban (Aggrastat): 12.5 µg per Kg

9.10.3. Post-Procedure Medication

- **P2Y12 Inhibitor**: Post implant, a 180 mg loading dose of ticagrelor (Brilinta) will be given through the NG or OG tube prior to the subject being awake. After the loading dose, 90 mg of ticagrelor twice a day (BID) will be continued for 72 hours.

- **Aspirin**: 81 mg of aspirin will be administered once a day (QD) for 72 hours post procedure. Aspirin 81 mg will be continued twice a day (BID) for a minimum of 6 months, provided that there are no new hemorrhages or contra-indication that arise at any point during the study or subject does not meet the antiplatelet reactivity testing requirements in **Section 9.10.3.1**.

Table 9-2. Medical Management Pre and Post Procedure

Pre-Procedure	No study-specific antiplatelet or anticoagulation agents will be given prior to device placement.
Intra-procedure	• General anesthesia medication per SOC • Medication administered during procedure, as applicable
Post-Implant Medication (Immediately after Pipeline™ Shield Device implant)	• Half loading dose (LD) of Glycoprotein IIb/IIIa inhibitor: o Eptifibatide (Integrilin): 90 µg per Kg OR o Tirofiban (Aggrastat): 12.5 µg per Kg
Post-procedure	• Ticagrelor (Brilinta) o 180 mg loading dose through NG tube or OG tube followed by, o 90 mg BID for 72 hours post procedure • Aspirin o 81 mg QD for 72 hours post procedure followed by, o 81 mg BID for a minimum of 6 months

9.10.3.1. Antiplatelet reactivity testing

Aspirin Reaction Units (ARU) test will be done at 24 - 48 hours post-procedure in each subject (after at least one dose of aspirin has been given and after the effects of Glycoprotein IIb/IIIa medication, eptifibatide or tirofiban, have dissipated)*. Subject(s) with ARU ≥ 550 units will be considered "non-responder(s)" to aspirin. For subjects who are non-responders to aspirin, $P2Y_{12}$ Reaction Units (PRU) test will be performed within 24 hours of the ARU test (after at least one dose of ticagrelor). PRU levels within

therapeutic range of ≥ 60 and ≤ 200 are acceptable. If subject's PRU levels are within the therapeutic range, subject will be given ticagrelor (90 mg BID) for a minimum of 6 months.

If PRU levels are outside the therapeutic range, the investigator will appropriately switch the maintenance dose of antiplatelet medication to clopidogrel (Plavix) 75 mg QD or prasugrel** (Effient) 10 mg QD for a minimum of 6 months after confirming the subject's responsiveness to either of these anti-platelet agents by repeated PRU tests, as needed. Note that prior to carrying out the PRU test and starting the maintenance dose, subjects should be administrated a loading dose of clopidogrel (600 mg) or prasugrel (60 mg).

**The half-lives of eptifibatide and tirofiban are approximately 2.5 hours and 2 hours, respectively (as per the most current labelling of eptifibatide and tirofiban).*

***Prasugrel (Effient) has a black box warning regarding bleeding risks and may be contraindicated in some subject.*

Prasugrel (Effient) Black Box Warning
Prescribing Information:https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s002lbl.pdf
WARNING: BLEEDING *Effient can cause significant, sometimes fatal, bleeding.* *Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke.* *In patients ≥ 75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered.* *Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.* *Additional risk factors for bleeding include:* • *body weight < 60 kg* • *propensity to bleed* • *concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs [NSAIDS])* *Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient.* *If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.*

9.11. Post Procedure

Subjects will be clinically assessed immediately after the procedure and will be evaluated on a daily basis for the occurrence of AEs and SAEs. General medical management should be carried out according to current AHA/ASA guidelines. For the post-procedure platelet reactivity testing and medication management please refer to **Section 9.10.3**.

9.11.1. 24 hours Post Procedure

The following 24 (± 12) hours post-procedure assessments shall be performed and recorded in the eCRF:

- NIHSS (conducted by a delegated qualified site study personnel)
- Glasgow Coma Scale
- CT or MRI imaging
- Review of concomitant medication
- Review of CIP specified medication
- Review of any adverse events
- ARU test 24 – 48 hours post procedure (and PRU test will be performed only for aspirin non-responders)

9.11.2. Prior to Discharge

The following post-procedure, prior to discharge, assessments shall be performed and recorded in the eCRF:

- DSA imaging
- Review of concomitant medication
- Review of CIP specified medication
- mRS assessment[1,2]
- Review of any adverse events
- Laboratory tests (CBC, CHEM-7, and coagulation profile)
- CT/CTA or MRI/MRA imaging, if done per standard of care (images should be submitted to the Core Lab
- COVID-19 testing, if done per SOC, data will be collected
- Clinical vignette at discharge[3]
- Discharge information (e.g., date of discharge, discharge disposition, days in the intensive care unit)

[1] mRS to be collected at discharge.

[2] mRS to be carried out by a certified independent assessor.

[3] If independent mRS assessor scores the mRS as ≥3, the investigator or physician involved in the management and care of the subject shall assess and document the subject's cause of disability.

9.11.3. Treatment Strategy – Staged Procedure

Prior to discharge, the subject will undergo conventional catheter-based angiogram (DSA) to assess for vasospasm. Due to the aneurysm morphologies that may be included in this study (e.g., blister aneurysms), careful placement of multiple Pipeline™ Shield Devices may be required to cover the aneurysmal vessel wall adequately. Additionally, due to the acute nature of ruptured aneurysms, placement of additional Pipeline™ Shield Devices after initial device placement may be required. Additional Pipeline™ Shield Devices, prior to subject discharge, may be placed across the lesion to achieve

adequate reconstruction and ensure aneurysm protection. In such situations, the same antiplatelet and anticoagulation regimen used during the index procedure will be followed.

Staged procedure may occur during the index hospitalization and is a treatment strategy therefore is not considered a retreatment, device/treatment failure, or a SAE. The day of last Pipeline™ Shield Device implant during index hospitalization (prior to discharge) will be considered as the Time 0 and will be the point of which follow up visit time windows will be calculated from. If no staged procedure occurs, then Time 0 will be the same date as Day 0 (index procedure). The staged procedure data shall be collected and recorded in the eCRF.

9.11.4. Aneurysm Occlusion Assessment

Post-procedure and follow-up angiograms will be reviewed to assess aneurysm occlusion according to the Raymond Roy Scale[127] (**Figure 9-2**).

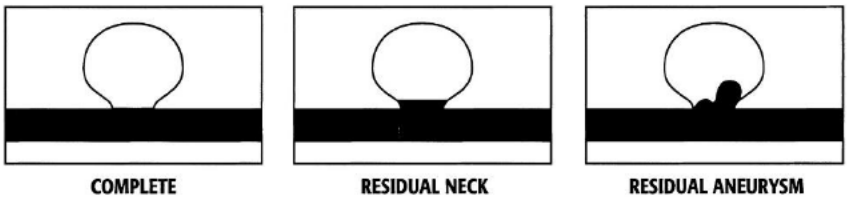


Figure 9-2. Raymond Roy Scale for Grading Aneurysm Occlusion

- **Class 1: Complete Occlusion** = Complete obliteration of the aneurysm
- **Class 2: Residual Neck** = Persistence of any portion of the original defect of the arterial wall as seen on any singe projection, but without opacification of the aneurysmal sac
- **Class 3: Residual Aneurysm** = Any opacification of the aneurysmal sac

9.12. Discharge

Subject will be discharged from the hospital as per standard practices. If the discharge date is expected to fall within the 30 day (± 14 days) follow up visit window, then the 30 day follow up assessments should be completed prior to the subject's discharge.

9.13. Retreatment

At the Investigator's discretion, the target aneurysm may be retreated at any time during the study. The retreatment procedure can occur any time after discharge from the index hospitalization or during index hospitalization if it is not related to the staged treatment strategy; and can include any endovascular or surgical intervention including another implant of the Pipeline™ Shield Device. In such situations, the date that the subject receives the initial Pipeline™ Shield Device implant (and not the date of the retreatment) will be considered Day 0. All retreatments will be recorded as an SAE.

The following retreatment procedure data shall be collected and recorded in the eCRF:

- Retreatment Procedure date
- Name of Primary interventionalist (implanting Investigator)
- Reason for retreatment
- Whether the retreatment was planned or unplanned
- Subject's radiation exposure (dose and fluoroscopy time)*
- Volume of contrast used
- Retreatment type
- Date of discharge
- If Pipeline™ Shield Device is used for retreatment, then device details of Pipeline™ Shield Device and microcatheter used (model number, lot number, and device disposition)
- Total number of devices, if multiple Pipeline™ Shield Devices are implanted

**Note: Investigator and site study personnel should take all necessary precautions to limit X-ray radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.*

A retreatment occurring after discharge from the index hospitalization will be considered an "Unscheduled Visit" and subjects will be required to undergo the study assessments detailed in **Section 9.15**.

9.14. Follow-up Evaluation and Visits

Subjects who consented and underwent a successful Pipeline™ Shield Device implant will undergo in-clinic, telephone or tele-video follow-up visits, as applicable, at 30 days, 90 days, 180 days and 365 days. All follow up visit time windows will be calculated from Time 0, which is the date of last Pipeline™ Shield Device implant during index hospitalization (i.e., date of the last device implant when staged procedure is performed). If a staged procedure did not occur, then Time 0 will be the same date as Day 0.

Subjects that had an unsuccessful implant procedure during the study per **Section 9.9.6**, are not required to return for the 30-day and 90-day visits but will be assessed at the 180-day visit unless subject is exited from the study prior to the visit. All required assessments at 180-day follow-up, except DSA imaging, should be completed.

Several clinical outcome measures were selected for this study:

- The **modified Rankin Scale (mRS)** is an overall assessment of global handicap. In the original Rankin Scale, a score of zero indicates the absence of symptoms and a score of 5, severe disability. The modified Rankin Scale adds a score of 6 for fatal outcomes. The mRS assessment at the scheduled follow up visits will be conducted by a certified independent

assessor. To become a certified independent assessor for mRS, the assessor should have passed a certification exam (or have evidence of a previous certification within the last 2 years). The assessor, once certified, will only be tasked with performing the mRS assessment for the study and will have no other responsibilities or duties associated with the study.

- The **National Institutes of Health Stroke Scale (NIHSS)** is a 42-point scale that quantifies neurologic deficits in 11 categories. Normal function without neurologic deficit is given a score of zero. The NIHSS assessment at the scheduled follow up visits will be conducted by a delegated qualified site study personnel.

At each follow-up visit described below, the respective study assessments shall be performed in-clinic or via telephone or tele-video, with the exception of imaging, which must be completed in-clinic. Data from the follow-up visits will be collected and recorded in the eCRFs.

9.14.1. 30 Day Visit

At day 30 (± 14 days) post Time 0, the following study assessments shall be performed and recorded in the eCRFs:

- Review CIP specified medications
- Review concomitant medications
- mRS assessment
- NIHSS assessment
- Imaging is not mandatory at 30-day visit. DSA, CT/CTA or MRI/MRA imaging, if done per standard of care should be submitted to the Core Lab.
- Review of adverse events
- COVID-19 testing, if done per SOC, data will be collected

9.14.2. 90 Day Visit

At day 90 (± 28 days) post Time 0, the following study assessments shall be performed and recorded in the eCRFs:

- Review CIP specified medications
- Review concomitant medications
- mRS assessment
- NIHSS assessment
- Imaging is not mandatory at 90-day visit. DSA, CT/CTA or MRI/MRA imaging, if done per standard of care should be submitted to the Core Lab.
- Review of adverse events
- COVID-19 testing, if done per SOC, data will be collected

9.14.3. 180 Day Visit

At day 180 (± 28 days) post Time 0, the following study assessments shall be performed and recorded in the eCRFs:

- DSA imaging (Note: Refer to **Section 9.9.6**, DSA imaging not required for subjects who had an unsuccessful procedure)
- Review CIP specified medications
- Review concomitant medications
- mRS assessment
- NIHSS assessment
- CT/CTA or MRI/MRA imaging, if done per standard of care (images should be submitted to the Core Lab)
- Review of adverse events
- Clinical vignette*
- COVID-19 testing, if done per SOC, data will be collected

*If independent mRS assessor scores the mRS as ≥3, the investigator or physician involved in the management and care of the subject shall assess and document the subject's cause of disability. If applicable, the 180-day clinical vignette will be completed at the 90-day post-stroke unscheduled visit.

9.14.4. 365 Day Visit

The completion of day 365 (± 56 days) post Time 0 visit will conclude the subject's participation in the study. The following study assessments shall be performed and recorded in the eCRFs:

- DSA imaging
- Review CIP specified medications if subject is still on antiplatelet therapy
- Review concomitant medications
- mRS assessment
- NIHSS assessment
- CT/CTA or MRI/MRA imaging, if done per standard of care (images should be submitted to the Core Lab)
- Review of adverse events
- COVID-19 testing, if done per SOC, data will be collected

9.14.5. Missed Visits

Every attempt must be made to have all subjects complete the scheduled follow up visits. Any subject who does not attend a scheduled follow-up visit should be contacted by site study personnel to determine

the reason for the missed appointment and to attempt to reschedule the visit within the visit window. If the missed visit was due to a serious adverse event (e.g., re-hospitalization), the serious adverse event must be reported in accordance to expedited reporting requirements detailed in **Section 11.3**.

9.15. Unscheduled Visit

An unscheduled visit includes any visits with the investigational site after the procedure that is not a scheduled follow-up visit (e.g. visits due to: retreatment, adverse event, 90-day post stroke assessment). The following study assessments shall be performed and recorded in the eCRFs:

- Reason for the unscheduled visit
- Review CIP specified medications if subject is still on antiplatelet therapy
- Review concomitant medications
- mRS assessment (if mRS assessment is carried out at an unscheduled visit 90 days post-stroke, the assessment should be carried out by a certified independent assessor)*
- NIHSS assessment*
- Imaging is not mandatory at unscheduled visit. DSA, CT/CTA or MRI/MRA imaging, if done per standard of care (images should be submitted to the Core Lab)
- Review of adverse events
- COVID-19 testing, if done per SOC, data will be collected

*NIHSS and mRS assessments will be required only for those subjects with any presumed events of neurological nature.

9.16. Recording Data

Study data will be collected using electronic case report forms (eCRFs) within a 21 CFR Part 11-compliant Electronic Data Capture (EDC) system. Data reported on the eCRFs must be consistent with the source documents and explanation for any data changes or deletions should also be entered into EDC.

The Principal Investigator is responsible for reviewing and ensuring accuracy and completeness of all eCRF data entries. The Principal Investigator will electronically approve the completed and verified eCRFs attesting to their review and agreement of the data entered.

Only delegated site study personnel who have completed the appropriate training for eCRF completion can enter data into eCRFs. Further guidance and instructions for eCRF completion can be found in the eCRF Completion Guidelines (CCGs).

9.17. Deviation Handling

A protocol deviation is defined as an event where the Investigator and the site study personnel did not conduct the study according to the Clinical Investigation Plan. Investigator and the site study personnel

may not deviate from the Clinical Investigation Plan, except under emergency circumstances to protect the rights, safety and well-being of human subjects.

All protocol deviations will be reported to the Sponsor within the study database and to the IRB/EC, as required by their reporting policies and procedures. When deviations occur, investigational sites are expected to assess and implement preventative and corrective actions to prevent further protocol deviations.

The Sponsor is responsible for routinely reviewing, analyzing and assessing the significance of all reported protocol deviations. Investigational sites with a high rate of protocol deviations or a trend in protocol deviations will be closely evaluated. If an investigational site demonstrates persistent protocol deviations, they may be prohibited from enrolling additional subjects, and in some cases, participation in the study may be terminated by the Sponsor.

9.18. Subject Exit, Withdrawal or Discontinuation

Subjects may withdraw from the study at any time without penalty or loss of medical care, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor. Subjects who withdraw/discontinue participation from the study will not be replaced.

Upon withdrawal from the study, the subject will be exempt from further data collection. All data collected up to the time the subject withdraws/discontinues participation in the study will remain in the study database and will be used for analysis. The reason for withdrawal/discontinuation shall be recorded in the eCRF and in the subject's medical record.

9.18.1. Lost to Follow-up

A subject will be considered lost to follow-up if the subject cannot be reached after a minimum of three (3) attempts to contact the subject for a follow-up visit. The site study personnel must document a minimum of three (3) attempts, and the final documented attempt should be made via registered letter.

9.18.2. Withdrawal by Subject

All enrolled subjects have the right to withdraw their consent at any time during this study.

Whenever possible, site study personnel should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. If the site study personnel are unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. Documentation of the subject's withdrawal will be provided to the Sponsor.

9.18.3. Subject Withdrawal by Investigator

Investigator may withdraw a subject from the study, with or without their consent, for any reason that in the Investigator's opinion could negatively affect the well-being of the subject, due to subject non-compliance, or if the IRB/EC or regulatory authority stops the study for any reason. If a subject is withdrawn from the study, the Investigator will promptly inform the subject and Sponsor.

9.18.4. Sponsor Request to Withdraw Subject

Subjects may be withdrawn at any time at the discretion of the Sponsor for safety or administrative reasons, or due to early termination of the study. Sponsor will notify the Investigator if the subject is to be withdrawn from the study.

10.Risks and Benefits

10.1. Potential Risks

Residual risks from the risk management workbook (RMW13-0001) for Pipeline™ Shield was analyzed to determine the potential clinical harms that may be associated with the use of the Pipeline™ Shield Device. Residual risks, as identified in the risk management work (RMW13-0001) are included in the below potential risks. Note that the Risk Management Workbook is a document that is continuously updated. The most current associated risks are also captured in the investigational IFUs (M009043CDOC2 (U.S.) and M031954DOC2 (Canada)). Anticipated adverse events and adverse device effects associated with use of the study device and the study procedure(s) include but are not limited to:

Neurological Events of Interest	An event of interest related to the target aneurysm clinical outcome and includes the following events of interest: Death Stroke Intra-Cranial Hemorrhage (ICH) Target Aneurysm Rebleed (Cerebral Aneurysm Rebleed After Treatment) Transient Ischemic Attack (TIA) Cranial Nerve Palsy Hydrocephalus Seizure Cerebral Refractory Vasospasm Cerebral Infarction Target Aneurysm Retreatment Visual Impairment
Procedural Events of Interest	Events representing the endovascular procedural complications of the study aneurysm treatment. Complications could be fatal or non-fatal, Serious or Non-Serious, Acute or Delayed. These include: Access Site Complications such as: o Hematoma o Inflammation o Infection o Necrosis o Pain and tenderness o Granuloma Associated Risks of Trans Radial Access such as: o Radial artery spasm o Radial artery perforation o Infection o Necrosis o Pain and tenderness o Compartment syndrome o Radial artery occlusion o Hematoma or hemorrhage o Sterile inflammation o Granulomas

	○ Hand Dysfunction ○ Amputation ○ Pathological hand cold intolerance Vascular Complications (Intra-Cranial or Extra Cranial) Thromboembolic Complications Anesthesia Related Complications Contrast Related Complications Excessive Radiation Complications Systemic Complications
Device related Events of Interest	Events representing complications of the study device or its use. These include fatal or non-fatal, serious or non-serious in nature: Device thrombosis Parent artery (Intra-Pipeline™ Device) Stenosis Incomplete occlusion of the aneurysm (at follow-up imaging) Mechanical device failures (Device Deficiencies) including but not limited to: ○ Incomplete Open ○ Failure to open ○ Push wire fracture and separation issues ○ Loss of device Integrity (fracture, fragmentation break) ○ Device- catheter interaction (excessive friction, trackability issues) ○ Device foreign body reaction (toxicity, granuloma) ○ Foreign body in patient ○ Device movement ○ Foreshortening (delayed) ○ Migration ○ Herniation into the aneurysm ○ Device twisting
APT Related Events of Interests	Events representing complications of the use of Antiplatelet Therapy. These include fatal or non-fatal, serious or non-serious in nature: Bleeding Complications (GUSTO) Thrombocytopenia/Thrombotic thrombocytopenic purpura Hemoptysis Epistaxis Allergic reaction to medications including angioedema Generalized Headache Dizziness Anemia Abnormal Liver and/or Kidney function Gastrointestinal (GI) Symptoms Dyspnea Fatigue Arrhythmia Note: For comprehensive potential risks associated with antiplatelet therapy, please refer to the most current labelling for the specific antiplatelet drug e.g., eptifibatide, tirofiban, ticagrelor, aspirin, prasugrel.

10.2. Risk Minimization

Several safeguards are incorporated into the study to minimize subject risk. All pre-clinical device testing

for the implantable braid and the single use delivery system are performed in accordance with regulations and recognized standards. All test results have passed the required specifications supporting reasonable safety for this clinical product.

At each investigational site, the study will be conducted under the direction of a qualified physician experienced with endovascular procedures including intracranial aneurysm repair and who will have a history of completing Pipeline™ Device cases in accordance to the Medtronic Medical Education Pipeline™ Device training program. All participating investigators have experience conducting clinical research and have adequate personnel to assure compliance to the Clinical Investigation Plan.

Subjects will be monitored closely as part of the study to allow for detection of adverse events, should they be present. This, in turn, should allow for early treatment, if necessary. Protected health information will not be collected on eCRFs or other study-related documentation to be provided to the Sponsor.

All study data will be monitored by individual site and by combining data from multiple sites. Clinical outcomes of all study subjects will be routinely monitored by the Sponsor during the course of the study. Safety endpoint related events will be reviewed and adjudicated by an independent Clinical Events Committee (CEC) and an independent Data Monitoring Committee (DMC) will provide oversight throughout the study. In the event of unforeseen or increased risks to subjects encountered during the course of the study, the study may be suspended or terminated.

10.3. Potential Benefits

Since the introduction of the Pipeline™ Embolization Device, flow diverters have represented a shift in interventional aneurysm treatment from endoluminal based approaches to vessel reconstruction. The Pipeline™ Embolization Device, when placed across the aneurysmal neck, redirects blood flow away from the aneurysm sac, leading to aneurysm thrombosis and occlusion. By disrupting the hemodynamic exchanges across the aneurysm neck and into the sac, the Pipeline™ Embolization Device addresses the diseased segment of the parent artery, allowing for neoendothelialization to occur, effectively excluding the aneurysm from the vessel wall.[76-78] The occluded aneurysm decreases progressively in size, resulting in a restructuring of the local neurovasculature to its pre-aneurysm state. In addition, since flow diverters are placed in the parent artery, they do not leave behind coil mass which may cause significant symptoms following treatment. Clinical study results and findings from the published literature report Pipeline™ Embolization Device and Pipeline™ Flex Device technical success rates of 87-100%.[96,98,99,101-103,122,162] Complete aneurysm occlusion is commonly measured using the Raymond Roy Scale.[127] Arteriographic outcomes are divided into three categories in this scale: (1) complete occlusion, (2) residual neck, and (3) residual aneurysm.[127] Pipeline™ Embolization Device treatment achieves up to approximately 95% permanent aneurysm occlusion.[32,33,93-97,122]

Aneurysmal rupture resulting in aSAH is an emergent condition. More than two third of patients hospitalized for aSAH in the United States do not receive treatment to secure a ruptured aneurysm.[57,58]

The mortality for patients who did not undergo treatment exceeds 30%;[9,57] and mortality rates as high as 95% were reported, with death in 76.9% (117/152) of patients during the hospital stay, and 85.5% at 3-month follow-up.[6] Only 5.7% (27/477) of conservatively managed patients were reported to have good clinical outcome.[163] Surgical treatment of ruptured aneurysms is associated with high mortality (12.5%-27.7%[6,57,75]) and disability of 34.8%[34]-38% of survivors.[75] Of endovascular treatment modalities, coiling, balloon-assisted coiling (BAC) or stent-assisted coiling (SAC) are used in 97.8% of cases,[73] and are associated with lower mortality (17.3%[6,57]) and disability (23.7%-33.1%[34,74,75]) than surgical clipping. However, these approaches cannot be used for some types of aneurysm morphologies, including giant, dissecting, fusiform, and blister ruptured aneurysms. Thus, flow diversion therapy with Pipeline™ family of devices offers a treatment of choice for patients with ruptured blister/fusiform/dissecting aneurysms for which standard techniques such as surgical clipping, coil embolization or stent-assisted coiling cannot be used.[25-29] High pore density in a flow diverter promotes progressive thrombosis and shrinkage of the lesion.[87]

Flow diversion is not the primary treatment of choice after aSAH because of the risk associated with dual antiplatelet regimens in the setting of acute rupture. Moreover, the performance of invasive procedures in the preprocedural or periprocedural period, which may include the placement of an external ventricular drain (EVD), central line, shunt, tracheostomy, and/or percutaneous endoscopic gastrostomy tube, as well as a craniotomy for evacuation of hematoma and decompression, carries additional risk for patients who are receiving dual antiplatelet therapy.[164]

In 2011, de Barros Faria et al.[165] from Argentina published their results after flow diversion in 23 patients with dissecting intracranial aneurysms, of which 52% had SAH. There were no aneurysmal ruptures after treatment in this series. Martin et al.[166] from Toronto published the first series consisting of only ruptured aneurysms treated with Pipeline™ Embolization Device. In 3 ruptured aneurysms they achieved aneurysm obliteration in all cases, with no hemorrhagic complications. Concurrently, McAuliffe and Wenderoth[167] reported 11 patients with recent aSAH treated with flow diversion at 3 Australian centers. Because two patients died of aneurysm rebleeding during the acute period, the investigators concluded that flow diversion should be used with caution in these cases, and coiling should be used if possible, to avoid re-rupture. However, in a series of 20 aSAH patients who underwent flow diversion, Cruz et al.[168] reported that one hemorrhagic complication occurred in a patient with a giant aneurysm treated with Pipeline™ Embolization Device and coils within 24 hours post implantation. Moreover, the IntrePED study showed that coiling in conjunction with Pipeline™ Embolization Device treatment required a significantly longer procedure (135.8 vs 96.7 minutes; P<.0001) and resulted in higher neurologic morbidity (12.5% vs 7.8%; P 5 .13).[169]

Delayed re-rupture is rare after a ruptured intracranial aneurysm treated with either coil embolization or surgical clipping;[170,171] however, early re-rupture of treated aneurysms occurs more frequently and has major consequences. In the Cerebral Aneurysm Re-rupture After Treatment (CARAT) study, the overall risk of re-rupture in the first year after treatment with coil embolization was observed to be 1.8%.

Similarly, the ISAT found a 1.7% risk of re-rupture in the first year. It was also noted that incomplete occlusion of the aneurysm was a strong predictor of risk of re-rupture and appeared to account for the difference in risk between clipped and coiled patients. Half of re-ruptures had occurred during the first 3 days after treatment. Also, there have been several reports of re-ruptures in aneurysms that have been completely occluded by surgery or endovascular therapy.[172,173] CARAT study, however, demonstrates that the risk of re-rupture is significantly lower after complete aneurysm occlusion and supports attempts to achieve this result.

A meta-analysis of 20 studies by Cagnazzo et al. that included 223 patients reported that even though only 32% of the ruptured aneurysms were occluded immediately after treatment, nearly 90% of the lesions had complete/near-complete occlusion during the 9.6 months of radiologic follow-up, with slightly higher occlusion rate (89%) for blister and dissecting/fusiform aneurysms compared with saccular lesions (79%).[16] Another meta-analysis by Madaelil et al. reported that 81% of patients with ruptured aneurysms treated with flow diverters had favorable clinical outcomes,[21] which is comparable to the number of patients with similar outcomes in large studies such as ISAT.[88] Cagnazzo et al. reported 17.8% flow diversion associated complications which mostly occurred in the periprocedural/early period after treatment, with a 7% treatment-related morbidity,[16] and Madaelil et al. reported composite rate of hemorrhagic or ischemic complication rate of 12%.[21] Cagnazzo et al. reported hemorrhagic complications in 7% of the patients[16] and Madaelil et al. reported a 9% composite rate of intracranial hemorrhagic complications in the meta-analysis, including 5% from aneurysm re-rupture and 4% from other causes.[21] Ischemic complications rates were reported to be 8%[16] and 4%.[21] Madaelil et al. suggested that flow diverter-based treatment may be more effective for small aneurysms.[21] Flow diverters may present a viable treatment option for ruptured intracranial aneurysms that are not readily amenable to first-line treatments such as coil embolization or clipping,[21] or when traditional treatment methods are unfeasible.[16,22]

Pipeline™ Shield Device is an enhanced version of Pipeline™ Embolization Device, the clinical benefits of which have been consistently demonstrated in multiple clinical studies.[30,32,78,93,94,96,97,119-122] Pipeline™ Shield Device implant is modified with an inert surface modification, Shield Technology™ (**Section 6.1.3**) that incorporates a durable, non-reactive material specifically designed to mimic human red blood cell membrane. In addition to reducing friction of the device within the microcatheter, the surface modification has demonstrated a significant reduction in in-vitro thrombogenicity.[43,44] AlMatter et al. opined that the surface modification (Shield Technology™) to reduce the inherent thrombogenicity of flow diverters is a promising recent advancement.[22] Thus, it is anticipated that the benefits achieved from the Pipeline™ Device should be at least maintained and may be improved with the addition of the Shield Technology™.

10.4. Risk Analysis

A thorough risk analysis was performed as part of design control recommendations of the Quality System

Regulation (21 CFR 820).

The primary risks to subjects in this study are associated with the presenting subarachnoid hemorrhage and recurrent hemorrhage from the index lesion, which can cause symptomatic deterioration of the subject or death (20% - 35%). These (and other) hemorrhagic risks (e.g., ventriculostomy drain placement and management) are exacerbated by the requirement for periprocedural heparinization and anti-platelet medications. While the current Clinical Investigation Plan certainly limits exposure to these agents in comparison to the currently available therapies, they are still required for a brief period of time as specified in the Clinical Investigation Plan below. Stroke secondary to either occlusion of the implanted Pipeline™ Shield Device or cerebral vasospasm is also a significant (approximately 10% - 20%) risk.

Average radiation dose with Pipeline™ Embolization Device treatment is 2.8±0.213 Gy.[174] Subjects receiving between 2 and 3 Gy of radiation may be subjected to skin and hair changes days to weeks after the procedure, although the majority of these proved to be self-limited. The dose threshold between subjects may vary substantially, even at similar radiation exposures due to biological variation and as such, there is no known threshold dose where 100% of the subjects will experience skin and hair changes. Even at low doses, increasing increments of exposure to ionizing, radiation has the potential to increase future cancer risk in a linear fashion. This risk seems to be quite low but the risk is not zero.[175]

All information concerning subjects will be kept confidential in accordance with all applicable laws and regulations. All subjects will be assigned with a unique identifier known as the subject ID #. Presentations or publications about the study will not include personal identifying information.

10.5. Risk-Benefit Rationale

For ruptured intracranial aneurysms which are untreated or managed conservatively, the mortality rate exceeds 30%,[9,57] and can be as high as 95%;[6] with good clinical outcome in only 5.7% of conservatively managed patients.[163]

In the 20 studies which reported on the treatment of acutely ruptured aneurysms with the Pipeline™ family of devices,[30,48,134-151] the reported mortality rates were 11.5%,[134] 10.5%,[30] 1/10,[137] and 2/10 patients;[138] 4 studies reported either no mortality[139,144,147] or no procedure-related mortality.[141] One study reported mRS decline in 5 of 11 patients,[139] and 1 study reported periprocedural complications in 19.2% of cases.[134]

Surgical treatment of ruptured intracranial aneurysms (RIAs), especially ruptured blister aneurysms is associated with high risk of intraoperative rupture and development of large lacerations on the parent vessel resulting in poor clinical outcomes.[176] Deconstruction of the parent artery is often, an unacceptable or suboptimal treatment strategy, particularly in the setting of SAH,[54,66-68] whereas reconstructive surgical treatment is hazardous, as the vessel often lacks the structural integrity to hold aneurysm clips, leading to very high rates of intra-operative rupture and a high risk of parent vessel stenosis or occlusion.[54,66-68] Reconstructive endovascular treatment using a traditional strategy of coil embolization is difficult in these

lesions due to structural anatomy and its associated risk of rupture and ischemia.[13,177,178] The Pipeline™ Embolization Device represents a promising treatment for this purpose.[85] However, treatment of RIAs with flow diversion does not always occlude the aneurysm immediately, leading to the potential risk of rebleeding.[179-181]

General procedural risks during the endovascular treatment of intracranial aneurysms include intracranial hemorrhage/re-hemorrhage, hematoma, aneurysm and vessel perforation, symptomatic thromboembolism (2% - 8%), distal embolization (due to coil herniation), and vessel injury.[182] Flow diverters and stent-assisted coiling for treatment of intracranial aneurysms are associated with procedural risks such as major ipsilateral stroke or neurological death, parent vessel or branch occlusion, delayed aneurysmal hemorrhage, ipsilateral intraparenchymal hemorrhage, and delayed rupture of treated aneurysms > 10 mm.[182] The use of transradial access (TRA) has been reported in the treatment of intracranial aneurysms (IAs)[183-206] and the access site complication rate for aneurysm treatment via TRA was 0%.[191,196-198,204,206] The rate of access site complications associated with TRA for neuroendovascular procedures ranged from 0%-2.85%.[183,190,191,193,194,196-198,203,204,206-217] The common access site complications reported were radial artery spasm,[203,216] radial artery occlusion,[203] infection at access-site,[215] slight ecchymosis around the puncture site,[210] and slight swelling/hemorrhage at the access site with no clinical significance or need for treatment.[190]

The potential risks associated with the use of the Pipeline™ Shield Device, based on risks observed with the Pipeline™ Embolization Device and Pipeline™ Flex Device, include ischemic stroke,[30,41,96,120,125,135,140,144,218-246] intracranial hemorrhage,[30,41,96,97,120,125,135,139,140,143,144,150,174,218,220,222,224-228,231-234,237,239-242,244,246-275] neurological deficit,[30,48,94,135,143,146,148,218,221,222,224,227-229,231-234,236,242,245,247,249,250,252,253,255,264,267,269-274,276-282] and death.[32,33,94,95,97,122,125,134,142,144-148,155,181,224,227,241,242,251,253,283-327]

A total of 56 studies reporting clinical outcomes in ≥ 25 patients observed 275 cases of ischemic stroke or cerebral infarction.[30,32,41,96,97,120,125,135,140,142-145,148,149,218-246,250,261,264,267,274,275,278,282,309,328-330] Of these, 37 studies reported ischemic stroke or infarction rates ranging from 0.80% to 9.4%.[30,41,96,120,125,135,140,144,218-246] The other nineteen studies reported ischemic stroke or cerebral infarction in 1/104,[145] 1/94,[261] 1/93,[250] 2/31,[32] 2/36,[97] 2/28,[142,227,238,288,328] 2/116,[278] 2/47,[328] 2/30,[329] 4/,[148] 7/109,[309] 36/793,[143] 4/36,[149] 1/35,[264] 3/52,[282] 10/29,[267] 21/553,[274] 1/123,[275] and 1/29[330] patients. Overall, nine studies reported that the events were procedure-related[227,229,231,234,238,241,274,275,328] and 3 studies reported an ischemic stroke that was device-related.[142,235,238] None of the other studies stated whether or not any of the cerebral infarction cases were attributed to the Pipeline™ family of devices. Overall, based upon the clinical evidence in the literature, ischemic stroke or infarction rates are low and the benefits of use of the Pipeline™ family of devices are expected to outweigh the risks.

Sixty-two studies reporting clinical outcomes in ≥ 25 patients observed 343 intracranial hemorrhages.[30,41,96,97,120,125,135,139,140,143,144,150,174,218,220,222,224-228,231-234,237,239-242,244,246-275] The rate of ICH

ranged from 0.6% to 16.7%.[30,41,96,120,135,139,140,143,150,174,218,220,222,224-227,232-234,237,239,242,244,246-248,250,257-262,264,265,268-273,309] Seventeen studies did not report the rate of ICH, and instead reported the number of ICHs; in 4/ 88,[251] 10/130,[249] 2/40,[241] 1/100,[144] 4/36,[97] 1/43,[253] 2/42,[254] 1/40,[125] 1/29,[255] 1/32,[228] 1/100,[231] 7/178,[240] 2/65,[266] 1/29 and 1/28,[267] 5/553,[274] 1/123,[275] and in 2/29[263] patients. Eight studies reported intracranial hemorrhage as procedure-related complication.[125,144,227,241,273-275,309] None of the other studies stated whether or not any cases of intracranial hemorrhage were attributed to treatment or the Pipeline™ family of devices. Overall, based upon the clinical evidence in the literature, intracranial hemorrhage rates are low and the benefits of use of the Pipeline™ family of devices are expected to outweigh the risks.

Forty-two studies reporting clinical outcomes in ≥ 25 patients observed a total of 140 cases of neurological deficit/dysfunction,[30,48,94,135,143,146,148,218,221,222,224,227-229,231-234,236,242,245,247,249,250,252,253,255,264,267,269-274,276-282] of which 19 studies reported neurological deficits ranging from 0.3% to 15.4%.[30,48,94,135,218,222,224,227-229,231,232,236,242,247,249,253,272,279] Seventeen studies did not report rates for neurological deficit/dysfunction, but reported the number of cases (n=51).[143,146,148,224,245,250,264,267,269-271,273,274,276-278,282] These studies reported 3/93,[250] 1/44,[224] 2/31,[146] 2/793,[143] 2/130,[148] 2/44,[276] 1/116,[278] 5/98,[277] 2/35,[264] 3/52,[282] 1/29,[267] 2/437,[269] 6/59,[245] 2/35,[270] 2/57,[271] 2/284,[273] and 2/553,[274] cases of neurological deficits. Transient deficits were reported in 3.0% (2/59)[245] 1.5% (1/67),[135] of cases, and in 2.8% (1/21),[270] 1.7% (1/57),[271] 5/52,[282] 2/29,[267] and 6/553,[274] patients. Five studies reported that the neurological deficits/dysfunction were procedure-related,[227,231,270,271,274] and 1 study reported that the neurological deficits/dysfunction were Pipeline™ Embolization Device-related.[273] None of the other studies reporting neurological deficits reported whether or not these events were device- or procedure-related. Overall, based upon the clinical evidence in the literature, neurological deficit/dysfunction rates are low and the benefits of use of the Pipeline™ family of devices are expected to outweigh the risks.

Fifty-nine studies reporting clinical outcomes in ≥ 25 patients observed a total of 292 deaths.[30,41,48,82,96,97,120,135-140,143,149,151,174,220,221,224,226,232-234,237,239,241-246,248,250-252,257-261,264-271,273,278,279,285,306,309,330-332] Of these, 44 studies reported mortality rates ranging from 0.5% to 27%.[30,41,48,82,96,97,120,135-140,151,221,224-226,232-234,237,239,242-245,247,248,250,251,257,259,260,265,268,271,278,279,306,309,331,333] Eight studies specifically stated that there was no mortality.[139,228,235,246,253,275,334,335] Seven studies reported death in 1/36,[149] 2/35,[264] 1/65,[266] 1/29,[267] 3/29,[330] 9/437,[269] and 1/35[270] of cases; and 1 study reported brain death in 1/284 of patients.[273] Overall, 2 studies reported that the events of death were procedure-related,[241,309] and 2 studies reported that death was device-related;[221,234] 3 studies specifically stated that deaths were due to causes not related to device or procedure,[48,267,330] 1 study stated that 6 patients of 9 mortality cases died from non-device-related causes,[259] and 1 study stated that no device-related mortality was observed.[138] None of the other studies stated if any of death cases were attributed to treatment or the Pipeline™ family of devices.

Pipeline™ Device Benefits

Successful treatment of conditions such as intracranial aneurysms prevents several risks and complications associated with these conditions; preventing these risks is beneficial to the patient. Overall, studies reported successful deployment of Pipeline™ family of devices at rates of 96.4% to 100%.[96,97,120,144,147,218,222,251,253,309] In studies that reported angiographic outcomes, complete or near complete aneurysm occlusion rates ranged from 52% to 100% at follow up durations ranging from 0.1 month to five years.[32,41,48,82,94,96,120,136,138,139,141,142,144,146,147,151,174,222,224,226-228,231,232,234-240,243,247-251,254,255,257,260,261,263,276,278,279,281,287,306,309,328,332-339] The overall retreatment rate with the Pipeline™ family of devices was low, ranging from 0.9% to 16%.[82,138,139,144,151,226,227,234,235,240,247,248,251,257,260,262,333,337] Good clinical outcomes (defined as mRS 0 - 2) ranged from 76.9% to 100% during clinical follow-up periods of 1 month to 5 years.[41,48,141,142,144,147,174,227,237-240,247,248,259,333,335,339]

Pipeline™ Device Benefits for RIAs

For ruptured intracranial aneurysms which are untreated or managed conservatively, good clinical outcome may be achieved in only 5.7% of patients.[163] Overall, in studies which reported on the treatment of acutely ruptured aneurysms using Pipeline™ Device,[30,48,134-151] complete occlusion rates were reported for 6/8,[138] 9/11,[138] 2/2,[142] 78.3% (18/23), and 83% (5/6)[144] of aneurysms at follow up durations of 5.9-10.1 months; and good clinical outcomes were reported for 70% to 80%,[48,134,138,141] and all of 2,[142] 2,[147] and 7[144] patients. Overall, in studies which reported on the treatment of acutely ruptured aneurysms using Pipeline™ Device,[30,48,134-151] complete occlusion rates were reported for 6/8,[138] 9/11,[138] 2/2,[142] 78.3% (18/23), and 83% (5/6)[144] of aneurysms at follow up durations of 5.9 - 10.1 months; months; and good clinical outcomes were reported for 70% to 80%,[48,134,138,141] and all of 2,[142] 2,[147] and 7[144] patients. The published literature provides evidence that the risk-benefit ratio of the Pipeline™ Embolization Device and Pipeline™ Flex Device is acceptable. The clinical benefits achieved with the Pipeline™ Embolization Device and Pipeline™ Flex Device for the endovascular embolization of intracranial aneurysms is significant and outweighs the individual and overall residual risk associated with its use. The addition of Shield Technology™ to the Pipeline™ Flex Device should enhance the deliverability and lower material thrombogenicity associated with the established Pipeline™ Flex Device based upon analogous thrombotic reductions seen in peripheral stent applications using a PC surface modification.

Pipeline™ Shield Device, Pipeline™ Embolization Device and Pipeline™ Flex Device share substantial equivalence in terms of indication for use, structural composition, construction materials, manufacturing process, safety, and performance.

Collectively, based on the extensive data with previous generations of the Pipeline™ family of devices, it is expected that the Pipeline™ Shield Device should provide a safe and effective treatment option for the treatment of patients with intracranial aneurysms. With the addition of the Shield Technology™, the potential to reduce material thrombogenicity improves upon the acceptable benefit-to-risk ratio that currently exists with the Pipeline™ Flex Device. Thus, in the treatment of acutely ruptured aneurysms that are not amenable to surgical clipping and coiling alone, the risks associated with the use of the Pipeline™

Shield Device are outweighed by the benefits of the device, demonstrating that the risk-benefit profile of the Pipeline™ Shield Device is acceptable.

11.Adverse Events and Device Deficiencies

All adverse events (AEs) will be collected and evaluated from the point of arterial puncture through study exit for all subjects enrolled in the study.

Investigators must obtain all information available to determine the causality, seriousness and outcome of the AE and to assess whether it meets the criteria for expedited reporting requiring notification to the Sponsor, and where applicable, regulatory agency(ies) and IRB/EC within the specified reporting timeframe per 21 CFR 812 and Canada Medical Device Regulations (SOR/98-282). Reported AEs shall be categorized by the Investigator when reporting to the Sponsor using the definitions provided in **Section 10.1**.

Signs and symptoms related to the target aneurysm that, in the opinion of the Investigator, existed prior to the point of puncture at the arterial access site on the day of the index procedure (Day 0) are not considered AEs and will be collected as Medical History unless the condition recurs after the subject has recovered from the pre-existing condition, or the condition worsens in severity, seriousness or frequency during the study.

If the subject is enrolled and undergoes puncture at the arterial access site but an attempt to deploy the Pipeline™ Shield Device is not made due to ineligibility of the subject for the study (i.e., procedural screen failure subject) any AEs that occur are to be collected through subject's study exit.

All adverse events should be documented in the subject's medical records and in the eCRF. At the time of study exit, all collected AEs with an outcome of "not recovered/not resolved," "recovering/resolving," or "unknown," must be reviewed and updated, as applicable.

A list of foreseeable AEs of the study is provided in **Section 10.1**.

11.1. Adverse Event Definitions and Classification

Anticipated adverse events and adverse device effects associated with use of the study device and the study procedure(s) are defined and classified in **Appendix II**.

11.1.1. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.

Note 2 to entry: This definition includes events related to the procedures involved.

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

(ISO 14155:2020 3.2)

11.1.2. Serious Adverse Event (SAE)

Adverse event that led to any of the following

a) death,

b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function including chronic diseases, or
3. in-patient or prolonged hospitalization, or
4. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

(ISO 14155:2020 3.45)

11.1.3. Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3 to entry: This includes '*comparator*' if the comparator is a medical device.

(ISO 14155:2020 3.1)

11.1.4. Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020 3.44)

11.1.5. Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note 1 to entry: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

(ISO 14155:2020 3.51)

11.1.6. Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

(21 CFR 812.3 (s))

11.1.7. Unavoidable Event

An event inherent to a surgical or endovascular intervention that is expected to occur in study subjects for a projected duration according to the Investigator's opinion.

Event Description	Timeframe (hours) from the endovascular or surgical intervention
Anesthesia related nausea/vomiting without headache or neck stiffness/pain.	24
Access site pain	24
Mild access site oozing	24
Peri-procedure catheter induced vasospasm that resolves without treatment.	0

Unavoidable Event does not require to be reported unless the event worsens or is present outside the stated timeframe post procedure.

11.1.8. Event Severity

The severity of an adverse event is a qualitative judgment of the degree of intensity, as determined by the Principal Investigator or as reported by the subject. The severity of the adverse event should be evaluated

according to the following scale National Cancer Institute (NCI) Adverse Event Severity Grading Scale – Common Terminology Criteria for Adverse Events (CTCAE):

- Mild: No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- Moderate: Some limitation of usual activities or specific therapy is required.
- Severe: Inability to carry out usual activities, hospitalization, emergency treatment, life-threatening events, or death.

11.1.9. Causality Assessment of Events

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:

- Use of the medical device for this study, Pipeline™ Shield Device
- Index procedure (on Day 0) involving initial application of the investigational medical device, and therefore not to any other procedures or treatments applied later during the clinical investigation (e.g., endovascular or surgical intervention to treat SAEs).
- Use of antiplatelet therapy.

The occurrence of each adverse event shall be assessed and categorized according to five different levels of causality (European Medical Device Regulation (2017/745)) for which the following definitions shall be used to assess the relationship of the adverse event to the investigational medical device, or index procedure, or use of APT:

1. Not Related:

   Relationship to the device or procedures can be excluded when:

   - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has no temporal relationship with the use of the investigational device or the procedures;
   - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2. 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.

3. 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.

4. Causal relationship:

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

   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that:
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on:

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

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

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

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

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the Sponsor remains uncertain about classifying the adverse event, it should not exclude the relatedness and classification of the event should be noted as “possible”.

11.2. Device Deficiency

Device Deficiency (DD) is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

(ISO 14155:2020 3.19)

The investigator should report these to the Sponsor (i.e., any Medtronic personnel), regulatory authorities and IRB/EC as required per local requirements.

When a DD is observed, every effort should be made to return the device and its packaging to the Sponsor in a timely manner.

11.3. Reporting of Events

The Investigator is required to report to the Sponsor all reportable SAEs, Device Deficiencies with SADE potential, UADEs, and USADEs within 72 hours after first learning of the event (**Table 11-1**). Where local country regulatory authorities require a more stringent definition or additional requirements, the Investigator should also comply with the local regulation. Additionally, the Investigator is also required to comply with their local safety reporting requirements per their IRB/EC.

The primary method of reporting SAEs to the Sponsor will be through the study database on the Adverse Event eCRF. If the study database is unavailable or inaccessible, the Investigator may send the information to the SAE email hotline. The Investigator shall complete data entry in the study database with the same information provided via the SAE email hotline as soon as the database becomes available.

UADEs/USADEs have expedited reporting requirements and must be reported by the Investigator to the Sponsor via email provided in **Table 11-1** within 72 hours and to the reviewing IRB/EC as soon as possible, but in no event later than 10 working days after the investigational site first learns of the effect (CFR 812.150(a)(1)). The primary method of reporting USADEs and UADEs to the Sponsor is through the SAE email hotline.

For adjudicable adverse events, the Investigator shall provide all available supporting source documentation, de-identified to subjects' identity and labeled with the study name and subject ID. In the event of a subject death, a copy of the death certificate or autopsy report, if available, should be sent to the Sponsor. If no source documents are available, the Investigator is requested to describe the circumstances of the subject's death in a letter, email, or other written communication to the Sponsor.

All device deficiencies that did not result in an adverse event should be reported to the Sponsor on the Device Deficiencies eCRFs in a timely manner. Device deficiencies that have the potential to cause a SADE shall be reported to the Sponsor within 72 hours of site study personnel's awareness of the event.

Table 11-1. Expedited Reporting Requirement for Adverse Event and Device Deficiencies

Serious Adverse Event (SAE) **Device Deficiency (DD) with SADE potential**	Investigational site will notify the Sponsor of all SAEs and DDs with SADE potential within 72 hours of being aware of the event. **Primary method of reporting**: Corresponding eCRF in study database.

	Secondary method of reporting: is dl.ELEVATESAEhotline@medtronic.com to be used in event that the study database is unavailable or inaccessible within required reporting timeline.
UADE/USADE	Investigational site will notify the Sponsor of all UADEs and USADEs within 72 hours of being aware of the event through the SAE hotline email: dl.ELEVATESAEhotline@medtronic.com

11.4. Processing Updates and Resolution

For any changes in status of a previously reported AE or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

11.5. Subject Death

All subject deaths must be reported by the investigator to the Sponsor on an AE eCRF (AE with outcome of death) within 72 hours after the investigator first learns of the death. In case of death, there should be one AE with the outcome of death.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Sponsor study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Sponsor study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Sponsor study team if available and allowed by state/local law. When the death occurs at another location, it is the investigational study site's responsibility to attempt retrieval of information about the death.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to investigational device and/or procedure
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

11.6. Product Complaint Reporting

A product complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market. Product complaint can be a result of misuse or abuse of the product:

- Abuse: Abnormal use (definition acc. #4.1 of MEDDEV 2.12-1)
- Misuse: Use error (definition acc. #4.20 of MEDDEV 2.12-1)

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the study and should be done in addition to the AE/DD reporting requirements. Refer to local regulations for reporting requirements.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by the Sponsor, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the Sponsor study team must be done according to the local Standard Operating Procedures. The Sponsor will notify the regulatory authority as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or country-specific investigational IFU which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

12.External Committees

To avoid and minimize bias, an independent Clinical Events Committee (CEC), PSC, Imaging Core Laboratory, and Data Monitoring Committee (DMC) will be in place to assess adverse events, assess eligibility based on imaging, perform imaging analysis and oversee subject safety, respectively.

12.1. Study Oversight

The Steering Committee shall be comprised of a minimum of 5 physicians who collectively have the qualifications and experiences in the field of neurology, radiology, neurosurgery, and/or interventional neuroradiology to provide expert medical guidance in the field of neurovascular clinical research.

The primary function of the Committee, as experts from the scientific research and medical community, is to provide guidance and expertise based on their everyday clinical practice and the evolving knowledge of the medical research community to advise on the design, conduct and scientific aspects of the Clinical Investigation Plan and throughout the course of the study.

Steering Committee membership, roles and responsibilities, and process/procedures will be carried out in accordance to their respective charter.

12.2. Clinical Events Committee Review

The Clinical Events Committee (CEC) shall be comprised of a minimum of 4 independent members (e.g., non-Medtronic employed physician), physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this study and will be responsible for an independent, objective and consistent review of adverse events.

The CEC will independently adjudicate each subject to pre-specified Events Of Interest (EOI) which include the primary endpoint, secondary safety endpoints, and pre-specified events of interest per **Section 10.1**.

The CEC can request additional source documentation and any imaging obtained in support of the adverse event to assist with adjudication.

CEC membership, roles and responsibilities, and meeting and adjudication process/procedures will be carried out in accordance to their respective charter.

12.3. Imaging Core Lab

The Core Lab will conduct independent analysis and assessment of subject images collected during the study. The Core Lab will provide qualitative assessments, which includes but is not limited to, defining aneurysm occlusion and parent artery stenosis, as it relates to the primary effectiveness endpoint, and to

analyze aneurysm and parent vessel characteristics, and device characteristics. Core Lab definitions and procedures will be detailed in the Core Lab Charter.

All images will be sent to the Core Lab including any additional imaging performed by the investigational site per standard of care.

12.4. Physician Screening Committee

The PSC shall be comprised of a minimum of 3 physicians who have the qualifications and experiences in the field of neurology, radiology, neurosurgery, and/or interventional neuroradiology. The PSC will be responsible for providing a partial subject eligibility assessment based on the imaging inclusion/exclusion criteria in addition to procedural compatibility assessment based on aneurysm anatomic morphology.

Imaging based eligibility will be determined per pre-procedure catheter-based angiography by the PSC prior to subject treatment with the Pipeline™ Shield Device.

PSC membership, roles and responsibilities, and process/procedures will be carried out in accordance to the PSC Charter.

12.5. Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) will be comprised of a minimum of three (3) independent scientific or subject matter experts which includes experts in the field of neurology, biostatistics/epidemiology, neurosurgery, and/or interventional neuroradiology. DMC membership consists of persons completely independent of Sponsor, research organizations, regulatory authorities, Institutional Review Board (IRB)/Ethics Committee (EC) and investigators involved in the study.

DMC will advise the Sponsor in regard to the continued safety of all subjects and to ensure the validity and scientific merit of the study. The DMC will exercise review of the overall safety of the study, periodically review of adverse events occurring in the study, and make recommendations to continue, modify, or stop the study, should any be considered necessary for safety or other related reasons.

DMC membership, roles and responsibilities, and process/procedures will be carried out in accordance to the DMC Charter.

13.Statistical Design and Methods

13.1. General Aspects of Analysis

A detailed Statistical Analysis Plan (SAP) will be finalized prior to performing any analyses and will expand upon the statistical methods presented below. Summary tables will summarize data for all subjects in aggregate. All recorded data will be presented in the individual data listings.

13.2. Analysis Execution

13.2.1. Analysis Sets

The results of this study will be presented using 2 populations defined as analysis sets.

The Intention to Treat (ITT) analysis set includes all subjects who were consented and in whom deployment of the Pipeline™ Shield Device was attempted (i.e., puncture at the arterial access site), independent of the procedure being completed successfully. The ITT analysis set will be used to evaluate all safety and effectiveness endpoints.

The per protocol analysis set will include all subjects that do not have an eligibility violation, are successfully implanted with Pipeline™ Shield Device, and receive the pre-specified regimen of post-procedural anti-platelet medications. This population will be used for secondary sensitivity analyses of the primary and secondary outcomes.

13.3. Interim Assessment for Sample Size Re-Estimation

An adaptive sample size re-estimation approach will be used in this study. This adaptive design will only allow for an increase in the sample size if the results are promising at the interim assessment; early stopping for effectiveness is not an option with this study design. The interim assessment for evaluation of the sample size will be predicated on the primary effectiveness and primary safety endpoints and conducted using a conditional power (CP) approach as described by Mehta and Pocock (2011).[53]

At the interim assessment, the CP for both the primary endpoints will be assessed when at least 50 subjects complete the 365-day evaluation or withdraw/die prior to the 365-day evaluation. If the CP for at least one of the primary endpoints is too low, the sample size will not be increased. If the CP falls in a range defined promising ($30\% \leq CP < 80\%$), then the sample size will be increased up to a pre-determined upper limit in order to increase the CP up to the 80% level. If an increase in the sample size is required for at least one of the two primary endpoints, and the re-estimation is within the defined sample size limits pre-specified by the CIP, the Data Monitoring Committee will communicate the revised target sample size to the study sponsor. Enrollment will continue towards the new target sample size, and the analyses performed by the Data Monitoring Committee will not be released to the study sponsor.

The Data Monitoring Committee will make one of following recommendations to the sponsor according to the interim results:

- Favorable: the interim results are sufficiently favorable that the study continues to the original sample size without the need to increase the study size
- Promising: the interim result is not disappointing, but it is not good enough. In this case the sample size is increased without exceeding pre-defined maximum sample size
- Unfavorable: the interim result is disappointing, and it is not worth increasing the sample size to retrieve CP. If unfavorable, there will not be a sample size recalculation and study will continue as planned.

13.4. Primary Endpoints

13.4.1. Primary Safety Endpoint

Primary Safety Endpoint:

Incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up.

H_o: Incidence of Neurological Death or Major Stroke through 365-days ≥ 35.0%

H_a: Incidence of Neurological Death or Major Stroke through 365-days < 35.0%

Success of the primary safety endpoint will be evaluated using a 1-tailed exact binomial test with a type 1 error rate of 2.5% based on ITT population.

The primary presentation of the results will be based on the observed data with multiple imputation for missing endpoint data.

13.4.2. Primary Effectiveness Endpoint

Primary Effectiveness Endpoint:

Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure

Primary Effectiveness Endpoint may also be referred to as "Composite Effectiveness Endpoint".

H_o: Percentage of primary effectiveness endpoint through 365-days ≤ 41.0%

H_a: Percentage of primary effectiveness endpoint through 365-days > 41.0%

Success of the primary effectiveness endpoint will be evaluated using a 1-tailed exact binomial test with a type 1 error rate of 2.5% based on ITT population. To claim study success, both primary safety and effectiveness endpoints should be met.

13.5. Secondary Endpoints

Secondary analyses will be conducted with the understanding that the results are for greater clarity ascribed to the procedure and the device and are not powered to detect a specific magnitude of difference. The detailed methods for summarization of the secondary endpoints will be included in the SAP.

There are 12 secondary endpoints as enumerated in **Section 4.1.2**.

13.6. Sample Size Determination

A total of up to 200 subjects may be enrolled (consented) to attain a target sample size of 100 evaluable subjects who will undergo treatment with available data up to 365 days. The minimum target sample size for this clinical investigation is 100 subjects (ITT population). The upper limit of up to 200 subjects to be enrolled (consented) accounts for a potential increase in the target number of evaluable subjects post-interim analysis and for a higher number of screen failures due to the emergent nature of this study in which subjects cannot be screened based on inclusion and exclusion criteria prior to arterial puncture and cannot be assessed by a PSC until after consent.

The sample size for this clinical investigation was based on the primary effectiveness and primary safety endpoints.

- Primary Effectiveness Endpoint: Complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure.

The test statistic for the hypothesis testing will be derived from a 1-tailed exact binomial test with a type 1 error rate of 2.5%. The expectation with the Pipeline™ Shield Device is that the incidence for the primary effectiveness endpoint will be significantly greater than 41%.

For effectiveness, testing against an a priori threshold of 41% with a power of 90% and a target type 1 error rate of 2.5% with the expectation of 58% of the subjects experiencing the primary effectiveness endpoint requires a sample size of 100 subjects. Based on the sample size estimation, the null hypothesis would be rejected if >=52 (upper critical value) subjects met the endpoint. The exact test was specified to derive the power in SAS. The actual type 1 error rate derived in the simulation was 1.70%. The calculated power was 90.6%.

- Primary Safety Endpoint: Incidence of major stroke in the territory supplied by the treated artery or neurological death through 365-day follow-up.

The test statistic for the hypothesis testing will be derived from a 1-tailed exact binomial test with a type 1 error rate of 2.5%. The expectation with the Pipeline™ Shield Device is that the incidence for the primary safety endpoint will be significantly less than 35%.

For safety, testing against an a priori threshold of 35% with a power of 90% and a target type 1 error rate of 2.5% with the expectation of ≤ 20% of the subjects experiencing the primary safety endpoint requires a sample size of 100 subjects. The exact test was specified to derive the power in SAS. The actual type 1 error rate derived in the simulation was 2.11%. The calculated power was 91.3%. The minimum target sample size for this clinical investigation is 100 subjects.

The target sample size for both the composite effectiveness endpoint and the safety endpoint is 100 patients. Based on the results of the interim assessment, the sample size could be increased if the results are promising based on the calculation of CP.

Justification for safety endpoint threshold

Systematic literature search was undertaken to evaluate all published literature on the treatment of unclippable **and** uncoilable ruptured intracranial aneurysms. Among 33 publications that were screened, either no relevant information assessing treatment of unclippable **and** uncoilable ruptured aneurysms was found or the sample sizes in the publications were inadequate for statistical evaluation.

Ruptured aneurysms that are unclippable and uncoilable have limited treatment options or no treatment options at all. Hence, a literature search on the natural history of untreated aneurysms was initiated using key words “ruptured”, “aneurysm”, “natural history” and “intracranial” which resulted in 213 articles. After screening, nine relevant publications were found describing the natural history of ruptured intracranial aneurysms that were either untreated or conservatively managed. Out of these nine publications, three publications with a minimum of 100 patients were obtained for further evaluation, Korja et al, 2017[9] (510 patients), Nishioka et al, 1984[10] (568 patients) and Sodhi et al, 2014[6] (152 patients). Together, these three publications reported data on 1,230 patients with ruptured intracranial aneurysms that were untreated. Note that the population included in these three natural history publications is similar to the population to be enrolled in the ELEVATE study as they have minimal or no other treatment options.

Additionally, data from three meta-analyses (Zhang et al, 2019[24], Zhang et al[23] and Li et al[12]) on patients with ruptured aneurysms treated with clipping or coiling were also considered for safety threshold determination. These meta-analyses were identified through search criteria for the effectiveness endpoint threshold, described below. Zhang et al, 2019[24], Zhang et al[23] and Li et al[12] reported data on 1004, 1408, and 11568, respectively; together, these three publications reported data on 13,980 patients.

The patient sample comprising the three meta-analyses includes those that can be treated with coiling or clipping and thus are not similar to the study population for ELEVATE which includes subjects that are not amenable to surgical clipping and coiling alone. However, in the absence of relevant published clinical data, these studies[12,23,24] were included as these are large meta-analyses that provide general mortality rates for ruptured aneurysms.

A summary of the mortality results by reference is broken down by (a) treated ruptured aneurysms and (b) untreated ruptured aneurysms. Note one of 3 articles on natural history (Sodhi et al, 2014[6]) also reported on 330 patients who did undergo treatment; this information has been added to the discussion on treated ruptured aneurysms.

Treated Ruptured Aneurysms:

Data from four publications, Zhang et al, 2019[24] (1004 patients), Zhang et al[23] (1408 patients), Li et al[12] (11,568 patients) and Sodhi et al, 2014[6] (330 patients), were evaluated. The four publications reported mortality rates of 1.8% - 17.4%[6,12,23,24] for endovascular coiling and 10.4% - 25.76%[6,12] for clipping.

In summary, mortality rates ranged between 1.8% to 25.76% for ruptured intracranial aneurysms treated with clipping or coiling. The most relevant statistic comes from the 330 treated patients in Sodhi et al (2014)[6]. The upper bound of the 2-sided 95% binomial confidence interval for 89/330 patients who died within 3 months of treatment is 30.83%.

UnTreated Ruptured Aneurysms:

Data from Korja (2017)[9], Nishioka (1984)[10] and Sodhi et al (2014)[6] were evaluated. The three publications reported mortality rates of 76.97%[6] at the end of hospital stay, and 65%[9] and 40.49%[10] at 6 months in 152, 510 and 568 patients with untreated or conservatively managed ruptured intracranial aneurysms, respectively.

In summary, there is a wide divergence among the reported results with mortality rates ranging from 40% to 77%[6,9,10] across the three articles on untreated or conservatively managed ruptured intracranial aneurysms. Based on these mortality estimates for patients who did not undergo treatment, 40% mortality at 6-months post-rupture would not be unexpected and is an extremely conservative estimate.

Safety Endpoint Threshold

The expectation with the ELEVATE study device is to achieve > 65% survival 365 days from the date of the intra-cranial rupture. The a priori threshold for statistical evaluation will be set at 35%.

In addition to survival, the primary safety endpoint definition includes major stroke, which has not been factored into the derivation of the a priori threshold, thereby making the 35% declaration a conservative estimate for testing.

Justification for effectiveness endpoint threshold

As described above, a systematic search for published literature on the treatment of unclippable **and** uncoilable ruptured intracranial aneurysms yielded no relevant publications with adequate sample sizes for statistical evaluation. Hence a literature search on treatment of all ruptured aneurysms between 2015 and 2019 was initiated using key words "ruptured", "aneurysm" and "intracranial" which resulted in 2050 articles. Due to the high volume of results, the literature search was filtered for meta-analyses with a minimum of 1000 patients and with treatments other than flow diverters. Based on these criteria, three relevant publications were obtained for further evaluation, Zhang et al, 2019, Zhang et al, and Li et al.

The primary effectiveness endpoint threshold for the ELEVATE study was derived based on reported rates of complete aneurysmal occlusion, stenosis, rebleeding and retreatment in patients with ruptured intracranial aneurysms as noted in **Table 13-1.**

Table 13-1. Data Analysis for Effectiveness Endpoint Derivation

ARTICLE	N	WEIGHTING FACTOR	OCCLUSION	OCC. WEIGHTED	STENOSIS	STENOSIS WEIGHTED	REBLEEDING	REBLEED WEIGHTED	RE-TREATMENT
Zhang 2019 Endovascular Treatment of Ruptured	1004	0.07236036	63.3	4.5804	15.4	1.1143	5	0.3618	Not Reported
Zhang 2019 Stent assisted coiling	1303	0.09390991	61	5.7285	8.4	0.7888	4.6	0.4320	16.6
Li 2012 Clipping	7230	0.521081081	84	43.7708	16.1	8.3894	1.1	0.5732	Not Reported
Li 2012 Coiling	4338	0.312648649	66.5	20.7911	20.9	6.5344	3	0.9379	Not Reported
	Sum: 13875	Sum: 1	Ave: 68.7%	Ave: 74.8709%	Ave: 15.2%	Ave: 16.8270%	Ave: 3.425%	Ave: 2.3049%	14.6%*

*The value 14.6% is the lower bound of the 2-sided 95% exact binomial confidence interval for retreatment obtained from Zhang et al, Journal of neurointerventional surgery. 2019;11(5):489-496

Weighted stenosis percentage (16.8270%), weighted rebleeding percentage (2.3049%) and the lower bound of the 2-sided 95% exact binomial confidence interval for retreatment (14.6%), were all subtracted from weighted occlusion percentage (74.8709%) to arrive at 41.14% as the threshold for primary composite effectiveness endpoint for the ELEVATE study. It is understood that the four events, complete aneurysmal occlusion, stenosis, rebleeding and re-treatment, may not be mutually exclusive; however, the data reported in the three publications regarding the four events are not separable and therefore treated as mutually exclusive for the purposes of this analysis. The outcomes reported in the above-mentioned publications are for all ruptured aneurysms, which include those that can be treated with clipping and coiling with traditionally established techniques. However, the patient population of the ELEVATE study is more challenging to treat since these patients have unclippable **and** uncoilable ruptured

intradural aneurysms and typically have minimal or no treatment options. Hence the objective performance criterion of 41% for the effectiveness threshold is justified.

Additionally, clinical experience regarding the treatment of unclippable **and** uncoilable ruptured intradural aneurysms was sought from the Steering Committee. Based on the outcomes for these specific sub-set of aneurysms they see in their clinical practice, the Steering Committee agrees with the 41% threshold for the primary composite effectiveness endpoint.

The expectation with the Pipeline™ Shield Device is to achieve primary effectiveness endpoint success in > 50% of the patients. Establishing an a priori threshold of 41% is an aggressive expectation where the observed incidence of success for the primary effectiveness endpoint would need to exceed the incidence from the peer-reviewed literature for clipping and coiling. This estimate is predicated on the assumption that the inability to coil or clip does not translate into a dampened expectation with the Pipeline™ Shield Device.

Additionally, the effect of the Pipeline™ Shield Device on mortality would need to be pronounced in order to have an incidence of composite endpoint success statistically greater than 41%. In order to have a reasonable chance of achieving the composite effectiveness endpoint, at least 50% of the patients must survive for 365 days. A sample size of 100 patients will yield a significant result for the primary safety endpoint if the mortality and incidence of major stroke is not greater than 24%.

Note that the primary effectiveness threshold of 41% and the primary safety threshold of 35% are substantially different from other trials on the Pipeline™ family of devices. This difference is based on the specific sub-set of subjects to be enrolled in the ELEVATE study *i.e.,* subjects with acutely ruptured wide-neck aneurysms not amenable to surgical clipping and coiling alone and thus have minimal or no treatment options. Note that several large studies have reported high mortality rates ranging from 65%-90% when patients with ruptured aneurysms are untreated.[6,9,10]

13.7. Missing data and Imputation methods

Every effort will be made to keep missing data, particularly the 365-day outcomes, to a minimum. Despite the investigational sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up (LTFU). The number and proportion of subjects eligible for, and compliant with, each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Since the 365-day effectiveness endpoint is based upon conventional angiographic follow up, the primary endpoint will be reported for all subjects who undergo the examination; all other ITT subjects without imaging will be treated as missing. This same approach will be used for the primary safety endpoint: the disposition of subjects who do not present for 365-day follow up and/or for whom no evidence is available regarding a major stroke in the territory supplied by the treated artery or neurological death will be treated as missing.

Missing data for the ITT population will be imputed using an iterative modeling approach via SAS PROC MI. Full details of multiple imputation methods will be described in the SAP.

13.8. Justification of Pooling

Heterogeneity across study sites will be assessed for the primary effectiveness endpoint using logistic regression with Firth's bias-reducing penalized likelihood.[340,341] The dependent variable will be the binary response, and study site will be included as a fixed effect. A type I error threshold of 0.10 will be used to identify whether variability in the outcome is explained by differences in study sites. If site is a statistically significant factor, further site-specific tests will be used to identify sites whose response rates differ substantively from other sites. Sensitivity analyses excluding these sites will be performed for the primary effectiveness endpoint. If the results of sensitivity analyses are consistent with the primary analysis, outcomes will be reported with all sites pooled. The pooling of U.S. and OUS sites will also be assessed using this approach. Full details will be included in the SAP.

13.9. Subgroup Analysis

Subgroup analyses will be performed based on aneurysm location and size. Additional subgroup analyses will be performed based on intracranial aneurysm morphology (e.g. fusiform, saccular) to evaluate the probability of occurrence of ischemic events in each subgroup following aspirin or antiplatelet agent discontinuation. Note that these subgroup analyses are not independently powered and they are for exploratory purpose only. Full details of factors and methods for subgroup analyses will be included in the SAP.

14.Ethics

14.1. Statement(s) of Compliance

This study will be conducted in compliance with the Clinical Investigation Plan, the Declaration of Helsinki (DoH), Canada Medical Device Regulations (SOR/98-282) and according to federal, national and local laws (including data protection laws), regulations, standards, and requirements within the jurisdiction where the study is being conducted. In addition, the study will be conducted in compliance with 21 CFR Parts:

- 11: Electronic Records, Electronic Signatures
- 50: Protection of Human Subjects
- 54: Financial Disclosure by Clinical Investigators
- 56: IRBs
- 812: IDEs

The principles of the DoH have been implemented through the IC process, EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy. It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the study and shall avoid improper influence on, or inducement of the subject, and all other parties participating in or contributing to the clinical investigation.

14.1.1. Sponsor Compliance

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

14.1.2. Investigator Compliance

The Principal Investigator (PI) assumes responsible for performance of the research study in accordance with the Clinical Trial Agreement, Investigator Statement, Clinical Investigation Plan, GCP, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IRB/EC. The PI shall be responsible for the day-to-day conduct of the clinical investigation as well as the safety and well-being of the human subjects involved in the clinical investigation.

Additional responsibilities of the PI include, but are not limited to:

- Ensuring IRB/EC approval is obtained prior to undertaking the study at the investigational site

- Ensuring informed consent is obtained per the methods and requirements by the investigational site's IRB/EC prior to non-standard of care study-related assessments and subject treatment with the study device
- Providing the Sponsor with accurate and complete financial information per 21 CFR Part 54
- Ensuring that all site study personnel assisting with the study are adequately informed and understand their study-related duties and functions

14.2. Institutional Review Boards/Ethics Committee

Institutional Review Board (IRB)/Ethics Committee (EC) must review and provide a copy of the written and dated approval prior to study commencement and subject enrollment. The Sponsor and/or Investigator must submit the Clinical Investigation Plan, Informed Consent Form and other pertinent documentation to the IRB/EC for review and approval and must also obtain renewal of IRB/EC approval, at minimum, annually or as mandated by local requirements, for the duration of the study.

The Investigator will provide the Sponsor with copies of all approvals and reports. Withdrawal of IRB/EC approval must be reported to the Sponsor immediately.

The study identifiers (e.g. Clinical Investigation Plan number, title, and version), documents reviewed and the date of the review should be clearly stated on the written IRB/EC approval. In addition, the approval letter should be accompanied by an IRB/EC roster, letter of compliance, or other documentation to allow verification that the Investigator, site study personnel, and/or Sponsor study team are not members of the IRB/EC. If identified as members of the IRB/EC, written documentation is required stating that he/she did not participate in the approval process.

Any amendment or modification to the Clinical Investigation Plan must be sent to the IRB/EC. The IRB/EC must also be informed of any event likely to affect the safety of subjects or the conduct of the study.

The Investigator will be responsible for fulfilling any additional requirements imposed by the IRB/EC (e.g. periodic safety reports and progress reports) and informing the Sponsor of any change in status of the IRB/EC approval. If any action is taken by an IRB/EC with respect to the investigation, that information will be forwarded to the Sponsor.

A list of the reviewing IRB/EC for each investigational site, including name and address, is maintained by the Sponsor study team and updated as needed.

15.Study Administration

15.1. Monitoring

15.1.1. Monitors

Appropriately qualified and trained personnel appointed by the Sponsor will conduct monitoring for each site at the start, during and closure of the study per the Medtronic Standard Operating Procedures (SOPs) and the Monitoring Plan. Monitors for the study will consist of Sponsor study team and/or qualified contract services appointed by the Sponsor.

The Sponsor study team, located at Medtronic Neurovascular, 5290 California Avenue, Irvine, CA 92617, will conduct and/or oversee monitoring for the study. A contact list including the name, address, and telephone number(s) of the Sponsor study team (e.g. Clinical Study Manager, Monitors and Medical/Safety representatives) will be provided to the site separately and will be maintained and updated as needed.

15.1.2. Monitoring Visits

Monitoring activities will be completed by the Monitor in accordance to the study-specific Monitoring Plan.

Prior to study participation, a site initiation visit will be conducted to confirm preparedness for Clinical Investigation Plan execution and investigational site facilities, to clarify the applicable regulations and requirements of the Clinical Investigation Plan, to review the process of implementing the Clinical Investigation Plan at the investigational site, to educate the Investigators on the device and to complete training of the Principal Investigator and site study personnel as designated on the site-specific delegated task list.

During the study, monitoring visits are conducted to complete source data verification, confirm accuracy of data, ensure study compliance, and perform investigational device accountability. During the monitoring visit, site study personnel shall be accessible to Monitor and the Principal Investigator will make all efforts to meet with the Monitor to review activities performed during the visit, including a review of any non-compliance issues identified and any action items. The Monitor will also review the Investigator Site File (ISF) to ensure presence and completeness of all study-related essential documents. Monitor must verify the Informed Consent Form, HIPAA authorization/data privacy and data release authorizations, where applicable, prior to reviewing subject data.

The Monitor will also ensure investigator and site study personnel are in compliance with applicable laws and regulations, Clinical Investigation Plan and IRB/EC procedures and policies. Any non-compliance that

is not adequately addressed by the Principal Investigator and site study personnel is cause for the Sponsor to suspend or terminate the investigational site.

Additional representatives from the Sponsor may be present during a monitoring visit or the endovascular procedure.

After each monitoring visit, the Monitor will send the Principal Investigator a follow up letter summarizing the monitoring visit. Additionally, the Monitor will draft a monitoring report that includes the date of the monitoring visit, the investigational site name, the names of the individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up and action items. The Principal Investigator will be responsible for ensuring that all follow-up and action items requiring resolution at the investigational site are completed in an accurate and timely manner.

A close-out visit will be conducted for each investigational site that completed a site initiation visit when enrollment at the investigational site has ended and all subject data has been collected. The purpose of the final visit is to collect all outstanding study essential documents, resolve any remaining open action items, ensure all data has been entered in the eCRFs, all queries are resolved and PI has signed off on the eCRFs, ensure ISF is accurate and complete, review record retention requirements with the Principal Investigator, final study device reconciliation, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

15.2. Data Management

Sponsor is responsible for compilation and verification of the study data, retention of the clinical study database, performance of statistical analyses, and preparation of the study reports. Sponsor will apply quality control measures to all stages of data collection and handling to ensure reliability and accuracy. In addition, the Sponsor will confirm that the data are processed correctly.

The Sponsor will ensure that the performance of Data Management activities occur in accordance with the study-specific Data Management Plan.

15.2.1. Data Quality Assurance

Data collection will be done by an electronic data acquisition method where all clinical data from enrolled subjects will be entered by a delegated site study personnel into a 21 CFR Part 11-compliant web-based Electronic Data Capture (EDC) system. The EDC system maintains an audit trail on entries, changes or corrections in the eCRFs.

All individuals who will be expected to use the EDC system will be given adequate training necessary to perform their assigned tasks as described in (21 CFR 11.10(i)).

All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

The EDC system will be reviewed and checked for omissions, apparent errors, and values requiring further clarification in accordance with the Data Management Plan. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only delegated site study personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

Monitoring will be performed in accordance to the Monitoring Plan to ensure quality and integrity of data and to identify any data fraud, data fabrication, and data errors. Sites will be evaluated in an ongoing manner to determine if there is a need to monitor more frequently or more thoroughly.

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. Only users with password-protected EDC access will have the ability to view study data within the secure EDC database. All attempts will be made to preserve subject confidentiality.

15.2.2. Data Ownership

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

15.3. Direct Access to Source Data/Documents

Investigator and site study personnel will maintain original source documents (e.g., medical and hospital records, progress notes) from which subject study-related data are derived. Information entered into the eCRFs will be verified against the source documents in accordance to the Monitoring Plan. Additionally, the Clinical Events Committee may require review of subject source documentation for AE adjudication. Source documents may be photocopied if required.

For purposes of auditing and monitoring, the Investigator agrees to allow Sponsor and their representatives, Monitors, auditors, and regulatory agency direct access to original subject medical records, including electronic medical records, certified copies of subject medical records or over-the-shoulder access to subject medical records.

15.4. Sponsor Audits & Regulatory Inspections

The Sponsor will secure an agreement with all parties to allow direct access, taking into account any restrictions due to local law, to all study-related data, source documents, and records, per **Section 15.3**, for the purpose of Sponsor audits and inspections by regulatory agencies.

Representatives of the Sponsor, independent of the employees involved in the clinical study, may conduct an audit of the study in compliance with regulatory guidelines and company policy. The purpose of an audit is to verify the adequate performance of the study-related activities.

Similar inspection procedures may also be conducted by agents of any regulatory body reviewing the results of the study in support of a regulatory submission.

The Investigator should immediately notify the Sponsor if he/she has been contacted by a regulatory agency or IRB/EC concerning an upcoming inspection.

15.5. Confidentiality

Protected Health Information of study subjects will be kept as confidential as possible in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any other data privacy laws, as applicable. Additionally, each subject participating in this study will be assigned a unique identifier.

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved who may have access to subject confidential information (e.g. Sponsors and its representatives, Monitors, IRB/EC, and regulatory bodies). All data shall be secured against unauthorized access.

Sponsor representative and auditors Monitors may have access to the study subject list and other information that personally identifies study subjects to ensure that data reported in the database corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, but is not limited to the subject's name, address, date of birth, and medical record number. All efforts will be made to ensure subject health information remain confidential in accordance with all applicable laws and regulations.

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

Privacy and confidentiality of information about each subject shall be preserved in study reports and in any publication.

15.6. Liability

The Sponsor is responsible for obtaining and maintaining appropriate insurance policies for the clinical study.

Provisions made for subject compensation and indemnification will be detailed in the Clinical Trial Agreement, as applicable.

15.7. CIP Amendments

During the course of the study, an amendment to the CIP may be necessary. Only the Sponsor is allowed to amend this CIP.

The Sponsor will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities and to provide a copy of the amendment to the investigational site for submission to the IRB/EC. Any submitted amendments or modifications must be approved by the regulatory authority and the IRB/EC prior to implementation at the investigational site, unless the modifications increase subject safety.

15.8. Record Retention

The Sponsor and Investigator shall maintain all study records and institute measures to prevent accidental or premature destruction of any data and/or documents related to the study.

The Sponsor and Investigator shall retain study records for a minimum period of two years, or longer in accordance with local law and regulations, after the latter of the following two dates: 1) the date on which the investigation is terminated or completed, or 2) the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

Investigator and/or site study personnel should contact Medtronic prior to the destruction of study records to ensure that they no longer need to be retained. If the Investigator is no longer participating in the study, the responsibility of conducting follow-up and maintaining records must be transferred to another responsible party within the institution. Notice of transfer must be provided in writing by the PI to the Sponsor and the IRB/EC.

15.9. Publication and Use of Information

Publication refers to all abstracts, articles, manuscripts, presentation and other forms of publication regarding the study data or results.

A Publication Committee will be formed and will be responsible for generating a Publication Plan. The Publication Plan will establish authorship criteria for publications for the study based on the study conduct

and compliance, contribution to the study design, management or enrollment, and willingness to accept the rights and responsibilities of an author.

The Sponsor intends to present and publish the results of this study. Participating Institution and Investigator will not independently publish, publicly disclose, present or discuss any results of or information pertaining to the study prior to the publication of the primary manuscript unless with explicit consent of the Sponsor and Publication Committee. All publications will be provided to Sponsor for review prior to submission or presentation.

The Sponsor will register and report results from the study into a public clinical trial registry such as ClinicalTrials.gov.

Participating subjects will not be identified by name in any study publications.

15.10. Suspension or Early Termination

If the study is terminated prematurely or suspended (e.g., if information becomes available that the risk to study subject is higher than initially indicated), the Sponsor will promptly inform all Investigators of the termination or suspension and the reason(s). The Investigator shall then promptly inform the reviewing IRB/EC and provide the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled subjects may be asked to complete all remaining study visits and/or be seen by the implanting physician according to standard of care following intracranial aneurysm treatment.

The Sponsor, IRB/EC or regulatory authority may decide to suspend or prematurely terminate an investigational site (e.g., in case of expiring approval of the reviewing IRB/EC, non-compliance to the CIP or lack of enrollment). If an investigational site is suspended or prematurely terminated, the Sponsor shall promptly inform the Investigator of the termination or suspension and the reason(s). The Investigator shall then promptly inform the reviewing IRB/EC.

16.Glossary

Term	Definition
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Note 3 to entry: This includes '*comparator*' if the comparator is a medical device. (ISO 14155:2020 3.1)
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1 to entry: This definition includes events related to the investigational medical device or the comparator. Note 2 to entry: This definition includes events related to the procedures involved. Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators. (ISO 14155:2020 3.2)
Aneurysm Maximum Diameter	Maximum diameter of the aneurysm dome in any direction.
Aneurysm Neck	Opening of the aneurysm where it meets the parent artery vessel.
Aneurysm Occlusion	Obliteration of the aneurysm with exclusion of the aneurysm cavity from the circulation. Further characterized according to the Raymond–Roy Scale[127]:

Term	Definition
	• Class 1: Complete Occlusion – Complete obliteration of the aneurysm. • Class 2: Residual Neck – Persistence of any portion of the original defect of the arterial wall as seen on any single projection, but without opacification of the aneurysmal sac. • Class 3: Residual Aneurysm – Any opacification of the aneurysmal sac.
Attempted Procedure	Any procedure where Pipeline™ Flex Embolization Device with Shield Technology™ ("Pipeline™ Shield Device") was attempted i.e., successful introduction of the Pipeline™ Shield Device into the microcatheter.
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020 3.19)
Dome-to-Neck Ratio[342]	Aneurysm dome max diameter (in any direction)/aneurysm neck width. For aneurysms without a defined dome (for e.g., fusiform), the dome-to-neck ratio will be considered as zero for the purposes of calculation.
Enrollment	Point at which the subject or subject's Legally Authorized Representative (LAR) signs the study authorized Informed Consent.
Fisher Grading Scale	Fisher Grading Scale[343,344] is used to predict the risk of cerebral vasospasm after subarachnoid hemorrhage (SAH).[345] **Fisher I**: No blood detected **Fisher II**: Diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) < 1 mm thick

Term	Definition
	Fisher III: Localized clots and/or vertical layers of blood ≥ 1 mm in thickness **Fisher IV**: Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots
Glasgow Coma Scale	Glasgow Coma Scale[346] is used to measure the state of a person's consciousness. <u>Eye Opening Response</u> • Spontaneous: 4 points • To speech: 3 points • To pressure: 2 points • None: 1 point <u>Verbal Response</u> • Oriented: 5 points • Confused: 4 points • Words: 3 points • Sounds: 2 points • None: 1 point <u>Motor Response</u> • Obeys commands: 6 points • Localising: 5 points • Normal flexion: 4 points • Abnormal flexion: 3 points • Extension: 2 points • None: 1 point
Hunt and Hess Scale	Hunt-Hess Classification of Aneurysmal Subarachnoid Hemorrhage[347] **Grade 1**: Asymptomatic, mild headache, or possibly nuchal rigidity **Grade 2**: Moderate-to-severe headache, nuchal rigidity, oculomotor nerve palsy but normal consciousness **Grade 3**: Drowsy or confused, mild focal neurological signs **Grade 4**: Stupor, moderate-to-severe motor signs **Grade 5**: Coma, moribund, and extensor posturing
Implant Success	Pipeline™ Shield Device implanted at the target site.
Index Procedure	The first intended procedure to implant the Pipeline™ Shield Device i.e., the first procedure with a successful

Term	Definition
	introduction of the Pipeline™ Shield Device into the microcatheter. The index procedure will be considered Day 0.
Informed consent	Informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative's) voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.
Institutional Review Board (IRB)/Ethics Committee (EC)	The IRB (United States) is any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. (21CFR56.102 (g)). Ethics Committee (EC) is independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. NOTE For the purposes of this International Standard, "ethics committee" is synonymous with "research ethics committee", "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region. (ISO 14155:2020 3.24)
Intention to Treat Population (ITT)	All subjects who were consented and in whom deployment of the Pipeline™ Shield Device was attempted (i.e., puncture at the arterial access site), independent of the procedure being completed successfully.
Investigator	An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (21CFR812.3 (i))

Term	Definition
Legally Authorized Representative (LAR)	An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102 (c)) (21 CFR 50.3 (1)).
Modified Rankin Scale (mRS)	Scale for measuring general neurologic function: 0- No symptoms at all 1- No significant disability despite symptoms; able to carry out all usual duties and activities 2- Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3- Moderate disability; requiring some help, but able to walk without assistance 4- Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5- Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6- Dead
mRS certified independent assessor	To become a certified independent assessor for mRS, the assessor should have passed a certification exam (or have an active certification). The assessor, once certified, will only be tasked with performing the mRS assessment for the study and will have no other responsibilities or duties associated with the study.
National Institute of Health Stroke Scale (NIHSS)[348,349]	Tool to quantify neurological impairment caused by stroke.
Per-Protocol (PP) population	The per-protocol population will include all subjects that do not have an eligibility violation, are successfully implanted with Pipeline™ Shield Device, and receive the pre-specified regimen of post-procedural anti-platelet medications. This population will be used for secondary sensitivity analyses of the primary and secondary outcomes.
Pre-screen Failure	A subject who did not meet eligibility and consent was not signed.
Procedural Screen Failure	An enrolled subject who was determined to be ineligible after arterial puncture per the pre-procedural

Term	Definition
	DSA imaging on the day of the index procedure prior to device implant.
Protocol deviation	Any study action taken by the Investigator or site study personnel in conflict with the Clinical Investigation Plan.
Screen Failure	An enrolled subject who was determined to be ineligible for the study prior to the arterial puncture on the day of the index procedure.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020 3.44)
Serious Adverse Event (SAE)	Adverse event that led to any of the following a) death, b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function including chronic diseases, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2020 3.45)
Stacking	Deploying Pipeline™ Shield Devices completely within each other (one inside the other) to increase the coverage density at the aneurysm neck.
Staged Procedure	The secondary procedure to implant additional Pipeline™ Shield Device(s) after the index procedure

Term	Definition
	but prior to discharge. The date of the last implant during the secondary procedure will be considered Time 0. Day 0 will be the day of the index procedure.
Target Aneurysm	Target aneurysm is the ruptured aneurysm determined by the treating physician to be the source of the subarachnoid hemorrhage (SAH).
Telescoping	Deploying Pipeline™ Shield Devices overlapping a minimum of one-third of each device's length into another device to create a construct (added length) anywhere within the treated artery.
Time 0	Date of the last Pipeline™ Shield Device implant during index hospitalization (i.e., date of the last device implant when staged procedure is performed). If no staged procedure occurred, then Time 0 will be the same date as Day 0. Follow up visit schedule will be based on Time 0.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3 (s))
Unavoidable Event	An event inherent to a surgical or endovascular intervention that is expected to occur in study subjects for a projected duration according to the Investigator's opinion.
Use Error	User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user Note 1 to entry: Use error includes the inability of the user to complete a task. Note 2 to entry: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Note 3 to entry: Users might be aware or unaware that a use error has occurred. Note 4 to entry: An unexpected physiological response of the patient is not by itself considered a use error.

Term	Definition
	Note 5 to entry: A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14971:2019 3.30)

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18. Appendices

18.1. Appendix I: Center for Medicare and Medicaid Services (CMS) IDE Study Criteria

Medicare beneficiaries may be affected by the device. Given the increasing percentage of the U.S. population that will qualify for Medicare in the coming decade as well as the four times higher prevalence of intracranial aneurysms among older adults, the trend toward an increasing number of endovascular procedures is very likely to continue.[350] Between 1996 and 2006, endovascular treatment of cerebral aneurysms increased from 20.1% to 67.0% per Medicare CPT codes.[350] In the PUFs study (**Section 3.3.1.2**) a total of 26.7% (30/114) of subjects enrolled were > 65 years old. This percentage is consistent with a study by Brinjikji et al[351] which found that between 2001 and 2008, from among the 34,054 patients >50 years old who underwent coiling of intracranial aneurysms, 29.3% (9,987) were > 65 years old. The number of patients in the United States who undergo treatment for ruptured aneurysm with endovascular coiling has increased dramatically between 2000 and 2006.[352] Twenty-three percent of patients undergoing clipping or coiling for ruptured aneurysm in the United States were 65 years of age or older.[353] ELEVATE study results are expected to be generalizable within the Medicare beneficiary population based on the prevalence of ruptured intracranial aneurysm in patients age 65 and older.

18.2. Appendix II: Adverse Event definitions and classifications

Anticipated adverse events and adverse device effects associated with use of the study device and the study procedure(s) are defined and classified below.

Term	Definition
Access site complications	
Access site Arterial Perforation	Patient complains of acute onset of pain with bleeding and hypotension when large defect. Contract injection may confirm extravasation of blood.
Access site Arteriovenous Fistula (AVF)	New bruit at the access site (thrill) with distal arterial insufficiency (steal phenomenon) with a swollen and tender, extremity (limb) due to venous dilatation detected either on the following day after sheath removal or at follow-up (when AV fistula of low volume) confirmed by color Doppler flow imaging and ultrasonography demonstrating an AVF with continuous systolic and diastolic flow.
Access Site Hemorrhage	Access site hemorrhage that requires diagnostic studies, extended hospitalization, or significant additional treatment (beyond e.g. compression or bandage) and/or that is associated with a drop of hemoglobin greater than 3g/dl and/or requiring blood transfusion/IV fluids.
Access site Infection	Local infection with fevers, chills and sometimes local reactions (such as phlebitis) with erythema, painful induration.
Access site Pseudoaneurysm (PSA)	An arterial rupture of one or more layers of its walls resulting in an encapsulated hematoma, which communicates with an artery. Classic finding is tender, pulsatile pulsatile mass with a systolic bruit, confirmed with duplex ultrasound. Angiography is unnecessary.

Term	Definition
Compartment syndrome	Excessive pressure buildup inside of a fascia-enclosed muscle space in the body and exerted against the local group of muscles, nerves, and blood vessels. The condition usually results from bleeding or swelling after an injury and is very painful and dangerous.
Hand Dysfunction	Disability, grip strength change, power loss, pathological hand cold intolerance or any other hand complication following radial artery access.
Local Neurogenic / Nerve Complications	Hypoesthesia, dysesthesia and/or hypoalgesia caused by compression of the nerve or as a result of hematoma from the artery access site.
Pain	Pain reported by the subject, specific to access site, which did not resolve within 24 hours post procedure or worsens or is present outside the stated timeframe of 72 hours post procedure.
Sterile inflammation	Inflammatory response that occurs in the absence of an infectious agent and occurs physiologically in response to any tissue injury as a part of the healing process. Sterile inflammation is initiated by non-infectious stimuli including physical damage to the tissue, necrosis, or foreign body reaction, and can be heightened in case of individuals with hypersensitivity to any of the products contained in the devices used for endovascular access. Sterile inflammation could manifest as localized redness, swelling and pain at the site of access without signs of infection.
Thrombotic Vessel Occlusion (peripheral)	Manifestation includes sudden or progressive pain, numbness, cyanosis, pallor, paresthesia. Clinical examination that reveals a cold ischemic limb with absent pulses. Condition may require duplex scans and arteriography for confirmation and to guide therapy.
Vessel Dissection	Physical separation of intima at the access site that results in exposure of internal arterial wall layers (media and/or adventitia) to blood. Confirmed by imaging.
Procedural complications	
Anesthesia Related Complications	Events related to anesthesia during study procedures (e.g. aspiration, hypotension, hypertension)
Contrast Induced Nephropathy (CIN)	An increase in serum creatinine as a result from the contrast used during the study procedure. • **Stage 1:** Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 µmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline. Urine output criteria: less than 0.5 ml/kg per hour for more than 6 hours • **Stage 2:** Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline. Urine output criteria: less than 0.5 ml/kg per hour for more than 12 hours • **Stage 3:** Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 µmol/l] with an acute increase of at least 0.5 mg/dl [44 µmol/l]). Urine output criteria: less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours.

Term	Definition
Contrast reactions	Contrast- Induced Complications: Complications arising due to the use of contrast agent used for imaging requirements during study procedure(s). • **mild reactions**: nausea, vomiting, cough, warmth, headache, dizziness, shaking, altered taste, itching, pallor flushing, chills, sweats, rash, hives, nasal stuffiness, swelling (eyes and face), anxiety • **moderate:** tachycardia/bradycardia, hypertension, generalized or diffuse erythema, dyspnea, bronchospasm, wheezing, laryngeal edema, mild hypotension. • **severe:** laryngeal edema (severe or rapidly progressing), convulsions, unresponsiveness, cortical blindness, cardiopulmonary arrest, profound hypotension, clinical manifest arrhythmias, anaphylaxis.
Systemic Complications	Systemic complications that result from the study procedure. May include: • **Infection**- Elevated body temperature (fever), and White Blood Count (WBC) > 12,000/ml, and Significant leftward shift on Differential caused by endovascular procedure and requires treatment. • **Organ impairment**- Partial loss of function, impairment, and/or damage of an organ that may resolve on its own, may require medical intervention or may lead to permanent or life-threatening injury when the organ impairment becomes critical (excluding the brain). • **Arrhythmia**- procedural related arrhythmia that requires medication • **Allergic reaction**- A mild to moderate to life threatening reaction to a procedural medication
Thromboembolic complication	Complication due to clot (thrombus formation) within the treated territory that is visualized on angiography during the study procedure, limits blood flow through the vessel under treatment and requires intervention or causes imaging changes (infarctions). Further categorization: • **Symptomatic**: Resulting in focal neurological status decline. • **Asymptomatic**: Resulting in no focal neurological status decline.
Unintended Radiation Exposure	Complications related to exposure to radiation during the endovascular study procedures. Will be characterized by: • **Cataracts**- Radiation induced cataracts. The current dose threshold is 2 Gy for a single dose or 5 Gy for a fractionated dose. • **Skin reddening, burn, ulcer**- Wounds caused by the acute or chronic effects of ionizing radiation and injury may involve the skin, underlying soft tissue, and even deep structures such as bone. • **Alopecia**- Geometric shapes of nonscarring hair loss related to the area of radiation. • **Bone marrow suppression** • **Late Appearing cancer**

Term	Definition
Vascular complication	• **Vasospasm**- Vasoconstriction observed during study procedure access or treatment with study device. • **Vessel Dissection**- Physical separation of intima during study procedure that results in exposure of internal arterial wall layers (media and/or adventitia) to blood. • **Vessel Perforation/Rupture**- A tear or hole through the vessel wall during the study procedure that results in blood extravasation. • **Vessel Occlusion (Intracranial)**- Angiographic evidence of intracranial vessel occlusion. • **Intracranial Fistula Formation**- Communication of the artery with the vein (e.g. carotid cavernous fistula). Each vascular complication will be further characterized by location into: • **Intra-Cranial:** observed within the cerebral vessel • **Extra-Cranial:** observed in the head and neck vessels e.g. External Carotid Artery • **Peripheral:** observed in the peripheral arteries e.g. femoral, radial, aortic etc.
Device related events of interest	
Branch Artery Stenosis	Degree of narrowing of any branches arising from the parent artery and/or arising from the adjacent vessel that are either completely or partially covered by the Pipeline™ Shield Device device(s). Stenosis will be classified as: • 5%-25% • > 25%- 50% • > 50% - 75% • > 75-95% • Angiographically occluded Note: 1%-<5% not discernable and high-grade stenosis > 95% is generally considered angiographically occluded. Each Branch Artery Stenosis event will be classified as follows: • **Asymptomatic**: No symptoms reported • **Symptomatic**: Symptoms reported
Device Deficiencies	Device deficiencies or failures including but not limited to. • **Incomplete open**- Evidence of Pipeline™ braid not fully open distally or proximally visualized under fluoroscopy • **Failure to open-** Pipeline™ braid failure to open after deployment, with evidence of under expansion with or without stretch visualized under fluoroscopy • **Push wire fracture or separation**- A break in the wire or connection point

Term	Definition
	that connects to the Pipeline™ device. • **Loss of device integrity**- Any perceptible fragmentation of the interstices of the devices. • **Device catheter interaction**- excessive friction, trackability issues • **Device foreign body reaction** - Issue associated with the chemical reaction between materials, usually metals or polymers and its environment that produces a deterioration of the metal/polymers or and its properties, which sometimes the detachment of small pieces of the coating film of a material. This may lead to inflammation or granuloma visualized by neuroimaging such as MRI or is identified during autopsies. • **Delayed foreshortening**- post procedure movement on either or both ends of the device in opposite direction towards the aneurysm neck. • **Migration**- Movement of device where both ends move in a single direction away from the aneurysm neck These events should be reported in the device deficiency CRF, unless they resulted in an Adverse event. If they resulted in an Adverse event, then only the AE CRF will be completed, and the device deficiency details will be collected within the AE CRF.
Device Thrombosis	Peri procedure, post-procedural, de novo formation of thrombus within the device visualized on imaging. Each Device Thrombosis event will also be reported with reference to symptoms reported for the subject: • **Asymptomatic**: No symptoms reported that are presumed to be related to the device complication. • **Symptomatic**: Symptoms reported that are presumed to be related to device complication.
Parent Artery Stenosis/In- Stenosis	Degree of narrowing of an artery and/or an adjacent artery in which the Pipeline™ Shield Device(s) was placed. This can be assessed in the region of Pipeline™ Shield Device placement on follow-up imaging. Stenosis will be classified as: • 5%- 25% • > 25%- 50% • > 50% - 75% • > 75-95% • Angiographically occluded Note: 1%-<5% not discernable and high-grade stenosis > 95% is generally considered angiographically occluded. Each Parent Artery Stenosis event will be classified as follows: • **Asymptomatic**: No symptoms reported • **Symptomatic:** Symptoms reported

Term	Definition
Target Aneurysm Retreatment	Any retreatment of the treated aneurysm after the primary study procedure implantation with the study device. These events will be further categorized by: • **Planned:** Retreatment procedure that is pre-planned (elective) and occurs in patients with no decline in neurological status. • **Unplanned:** Retreatment procedure that is either treatment emergent or occurs in patients with decline in neurological status. In addition to the possible cause of the Treated Aneurysm Retreatment, the following categories shall be adjudicated: • **Residual Aneurysm** – Incomplete occlusion, apparent flow in the aneurysm sac as defined by Scale of Roy • **Residual Neck** – Partial occlusion, some flow or eddying flow in the aneurysm sac as defined by Scale of Roy • **Aneurysm Increases in Size** • **Device Movement** – implanted study device movement following deployment, noticed at a follow up time point. o **Delayed foreshortening**- post procedure movement on either or both ends of the device in opposite direction towards the aneurysm neck. o **Migration** - Movement of device where both ends move in a single direction away from the aneurysm neck o **Herniation into aneurysm -** The Pipeline™ Embolization Device (PED) can foreshorten or stretch in vivo. Occasionally, unfavorable foreshortening of the device with proximal migration of the device can result in herniation of the proximal or distal end of the device into the aneurysm sac. o **Aneurysm Rupture** – Any rupture of the target aneurysm o **Insufficient Neck Coverage**-Neck is not fully covered o **Inadequate Deployment** – study device not deployed as expected. o **Indeterminate** – Unable to determine due to lack of information.
Neurological events of interest	
Cerebral Edema	• **Minor cerebral edema** - Accumulation of fluid in the intracellular or extracellular spaces of the brain. • **Malignant cerebral edema** - Massive accumulation of fluid to produce brain tissue shifts and herniation.
Cerebral Infarction	Cerebral ischemic changes found on imaging. Further characterized as: • **Asymptomatic**- Not associated with focal neurological deficit symptoms (i.e., silent infarctions*) • **Symptomatic**- Focal neurological dysfunction with transient** symptoms persisting less than 24 hours.

Term	Definition
	Cerebral infarction will be further classified as: • Ipsilateral- Same hemisphere as treated territory • Contralateral- Opposite hemisphere from the treated territory • Bilateral – Both hemisphere involved *Silent cerebral infarction: Evidence of new ischemic changes (infarction) on imaging with no associated focal neurological deficit symptoms **Cerebral Infarction with Transient Signs: Evidence of new ischemic changes (infarction) on imaging with focal neurological deficit symptoms lasting less than 24 hours.
Cranial Nerve Palsy	A decreased or complete loss of function of one or more cranial nerves. The sensory and motor innervation of the eyes originate from 6 paired cranial nerves. • **CNII**: optic nerve which is purely sensory in the eyes. • **CNIII**: oculomotor nerve which is responsible for innervating the major extraocular muscles of the eyes • **CN IV**: trochlear nerve which also contributes to the motor function of the eyes • **CN V**: trigeminal nerve has 3 main branches. The ophthalmic branch, maxillary branch and mandibular branch but only the ophthalmic branch provides sensory innervation to the eye. • **CN VI**: abducens nerve is the lateral rectus muscle of the eye and it causes the eye to abduct. • **CN VII**: Facial nerve which provides innervation to the muscles of facial expression and supports eyelid protraction, salvation, and the taste to 2/3rd portions of the tongue.
Death	• **Neurological Death:** Any subject death where the primary cause is identified as neurological resulting from direct consequence of ischemic stroke, hemorrhagic stroke or undetermined cause of stroke, or direct consequence of intracranial hemorrhage, encephalopathy, brain abscess, meningitis (excludes death from trauma brain injury, brain tumors). This also includes all deaths that are sudden or unwitnessed or deaths of an unknown cause, including deaths where a neurological cause cannot be ruled out. Neurologic death will further be classified as: o death due to proximate neurovascular cause (e.g. initial underlying neurologic condition) o death due to procedure related events o death due to device related events o death that is sudden or unwitnessed o death of unknown cause • **Non-neurological Death**: Any death where the primary cause of death is

Term	Definition
	clearly related to another condition (trauma, cancer, suicide)
Delayed Cerebral Ischemia (DCI)	Symptomatic vasospasm marked by the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total core or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies.
Headache	Headache that is new or worsening from baseline. Characterized by: • **Ipsilateral:** presumed treated vascular territory • **Contralateral**: not in presumed treated vascular territory • **Generalized:** pain not isolated to a specific location • **Indeterminate:** unable to determine due to lack of follow-up information
Hydrocephalus	The accumulation of excessive amounts of cerebrospinal fluid (CSF) within the ventricles of the brain, resulting from blockage or destruction of the normal channels for CSF drainage. Further classify as – • **Acute Hydrocephalus** – 3 days into the course of SAH • **Chronic Hydrocephalus** – after 2 weeks into the course of SAH
Intra-Cranial Hemorrhage	Hemorrhage within the fixed vault of the cranium (skull). ICH will be further categorized as: • **Intracerebral Hemorrhage**: Bleeding within the cerebral matter (brain parenchyma), not involving the ventricles. • **Intra-Ventricular Hemorrhage (IVH):** Bleeding within the brain ventricles. • **Sub Arachnoid Hemorrhage (SAH**): Bleeding into the subarachnoid space- the area between the arachnoid membrane and the pia mater surrounding the brain. • **Subdural Hematoma (SDH):** An extracerebral hematoma that is located between the dura mater and in the arachnoid layer of the meninges and does not expand into the subarachnoid space or the basal cisterns. • **Epidural Hematoma (EDH):** A rapidly accumulating hematoma between the dura mater and the cranium. In the event that a single hemorrhage event results in bleeding in multiple locations, the most severe category or primary hemorrhage should be selected. **Hemorrhage Location** will be noted as:

Term	Definition
	• **Treated Vascular Territory** – presumed origin of the treated vascular territory. • **Not in Treated Vascular Territory** – not in presumed origin of the treated vascular territory. • **Indeterminate** – Unable to determine due to lack of follow up information. Each **ICH etiology** shall be further classified as: • Due to Target Aneurysm Rupture • Due to Non-Target Aneurysm Rupture • Due to Hemorrhagic Transformation of core ischemic infarct • Hemorrhagic Due to Other Causes
Seizure	**Seizure:** Neurological disorder characterized by sudden and involuntary skeleton and muscular contractions (convulsions) with or without lapse of consciousness. Seizures can be partial or generalized. • **Partial:** A seizure that originates in a localized part of the cerebral cortex, that involves motor, sensory, autonomic, or psychic symptoms (such as twitching of muscles, localized numbness, or auras), and that may progress to a generalized seizure • **Generalized:** A generalized onset seizure is when both hemispheres (potentially asymmetrically) are activated at onset of the seizure, according to behavior and EEG. **Status Epilepticus**: Status epilepticus (SE) is a life-threatening state of ongoing or repetitive seizures may lead to permanent brain damage or death.
Stroke	A new focal neurological deficit of presumed vascular origin persisting ≥24 hours from symptom onset with or without neuro-imaging findings or other quantitative study that does not indicate a different etiology. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours. The definition includes: • Subjects presenting with clinical signs and symptoms suggestive of SAH and intracerebral hemorrhage. • Subjects presenting with cerebral ischemia • Sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli. The definition excludes: • Slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth. • Stroke events in cases of blood disorders such as leukemia or external

Term	Definition
	events such as trauma. Stroke severity will be graded as: • **Major Stroke**: A stroke, which is present for≥24 hours and increases the NIHSS of the subject by ≥ 4. • **Minor Stroke**: A stroke, which is present for ≥ 24 hours and increases the NIHSS of the subject by ≤ 3. NIHSS will be documented at the time of presenting with Stroke Symptoms and 24 hours later. Stroke Etiology will be noted as: • **Ischemic**: when the primary cause of the stroke is ischemic • **Ischemic with hemorrhagic conversion** • **Hemorrhagic**: Stroke occurring following an aneurysm rupture or rapidly progressing sub-arachnoid or intra-parenchymal hemorrhage. Stroke Outcome will be noted with respect to mRS (assessed at a minimum of 90 days post stroke event): • **Disabling**: mRS with poor functional outcome i.e. ≥3 points • **Non-Disabling**: mRS with good functional outcome 0-2 points • **Unknown**: Stroke occurs during index hospitalization prior to the 30d mRS assessment to determine mRS impact of baseline SAH, and therefore the contribution of new stroke event to mRS is not known. Each stroke will also be categorized by location: • **Treated vascular territory** • **Not in treated vascular territory**
Target Aneurysm Recurrence	Evidence of change in aneurysm occlusion status (from complete occlusion to residual aneurysm/neck) on DSA imaging compared to a previous DSA imaging.
Target Aneurysm Rupture	Any rupture of the target aneurysm. This will be further characterized as: • **Intra-Procedural**- occurring during the index procedure. • **Post-Procedural**- occurring any time after the procedure.
Transient Ischemic Attack (TIA)	Focal neurological deficit symptoms lasting ≤24 hours with no evidence of cerebral infarction.
Visual Symptoms	All visual symptoms that appear as either a worsening from baseline or as a new event. • **Scintillations**- bright lights, swirls in the eyes like spots, or shooting stars (photopsia). These episodes are intermittent. • **Scotoma**- spot in visual field where vision is absent or deficient

Term	Definition
	• **Photophobia**- abnormal sensitivity to light • **Blurred Vision**- blurry vision • **Eye Floaters**-temporary clumpy obstruction of vision • **Diplopia**- double vision • **Vision loss**- Loss of the ability to see • **Visual Field Deficit**- e.g. hemianopia • **Visual Disturbance**- not specified Visual symptoms will be further classified as: • **Ipsilateral***- Same hemisphere as treated territory • **Contralateral**- Opposite hemisphere from the treated territory *Ipsilateral Territory: Presumed to be of the vascular origin of the treated vascular territory
Antiplatelet events of interest	

Bleeding Complications	Any bleeding event including but not limited to:
	• Ecchymosis- bruising
	• GI symptom- GI bleeding
	• Anemia- low hemoglobin
	• Thrombocytopenia- low platelet count
	• Hemoptysis- coughing up blood
	• Epistaxis-nose bleed
	• Hematuria- blood in urine
	• Petechia- Bleeding from the capillaries into the skin or mucous membranes, which results in tiny (pinpoint) red marks.
	Bleeding complications shall be adjudicated using the GUSTO and BARC bleeding criteria which includes categorizing all bleeding events into the following categories:
	GUSTO
	• Severe or Life-threatening:
	  ○ Intracerebral hemorrhage
	  ○ Resulting in substantial hemodynamic compromise requiring treatment
	• Moderate: Requiring blood transfusion but not resulting in hemodynamic compromise

Term	Definition
	• Mild: Bleeding that does not meet above criteria **BARC** Type 0 No bleeding Type 1 Bleeding that is not actionable and does not cause the patient to seek treatment Type 2 Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional Type 3 a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision Type 4 a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)
Miscellaneous adverse events	
Acute Delirium	A common clinical syndrome characterized by inattention and acute cognitive dysfunction.
Acute Urinary Retention	A urologic emergency characterized by the sudden inability to urinate combined with suprapubic pain, bloating, urgency, distress, or, occasionally, mild incontinence.
Altered Mental Status	Changes in consciousness. I.E. Decreased level of consciousness, change in awareness, or Glasgow coma score.
Aphasia	Loss of comprehension or production of language.
Aspiration Pneumonia	Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and the lower respiratory tract. Radiographic findings include infiltrates in gravity-dependent pulmonary segments (superior lower lobe or posterior upper lobe segments, if the patient is in a supine position during the event, or basal segments of the lower lobe, if the patient is upright during the event).
Confusion	The state or condition of not being aware of or oriented to time, place, or oneself.

Term	Definition
Congestive Heart failure	A chronic, progressive condition in which the heart muscle is unable to pump enough blood through the heart to meet the body's needs for blood and oxygen. Heart failure usually results in an enlarged heart.
Deep Vein Thrombosis (DVT)	Lower limb pain and swelling caused by a thrombus and confirmed by venous ultrasonography of the lower limb.
Dysphagia	Difficulty swallowing. It usually affects the throat or the esophagus.
Electrolyte Imbalance	When the concentration of the specific electrolytes falls outside the normal range.
Embolism	A sudden obstruction of a blood vessel by debris. Blood clots, cholesterol-containing plaques, masses of bacteria, cancer cells, amniotic fluid, fat from the marrow of broken bones, and injected substances (such as air bubbles or particulate matter) all may lodge in blood vessels and obstruct them.
Fever	A symptom associated with a variety of diseases and disorders, characterized by body temperature above normal (98.6 degrees Fahrenheit, or 37 degrees Celsius); considered very serious at 104 degrees Fahrenheit (40 degrees Celsius) and higher.
Hospital Acquired Pneumonia	Pneumonia acquired ≥48 hours after hospital admission.
Hyperglycemia	Hyperglycemia is blood glucose greater than 125 mg/dL while fasting and greater than 180 mg/dL 2 hours postprandial.
Hypertension	Persistent elevation of blood pressure greater than 140/90 mm Hg.
Hypertensive urgency	Severe elevation in blood pressure (BP) without acute target organ damage. Systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg.
Hyponatremia	A decrease serum Na+ concentration (<134 mEq/L) that produces a hypotonic state with a decrease in effective osmolarity.
Hypotension	Hypotension is a decrease in systemic blood pressure below 90/60 mm Hg.
Hypoxemia	A reduction in the amount of oxygen (O2) dissolved in plasma (PaO2, where lower case “a” means arterial).
Inflammation	The reaction of blood -filled living tissue to injury with the following changes are seen locally: redness, swelling, heat, pain and loss of function.
Insomnia	Clinical condition characterized by difficulty initiating or maintaining sleep, accompanied by symptoms such as irritability or fatigue during wakefulness.
Leukocytosis	An abnormally large number of leukocytes, as observed in acute infection, inflammation, hemorrhage and other conditions.
Limb Ischemia	Ischemic rest pain, ischemic ulcerations, or ischemic gangrene resulting in hemodynamically compromised limb perfusion.
Mass Effect	A mass effects exerted by any mass, including, for example, an evolving intracerebral hemorrhage presenting with a clinically significant hematoma.

Term	Definition
	The hematoma can exert a mass effect on the brain, increasing intracranial pressure and potentially causing midline shift or brain herniation.
Meningitis	Inflammation of the meninges, the membrane covering the brain and spinal cord.
Metabolic Encephalopathy	Alteration in consciousness caused by diffuse or global brain dysfunction from impaired cerebral metabolism.
Migraine	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another International classification of headache disorders (ICHD-3) diagnosis.
Myasthenia Gravis	A disease of the neuromuscular junction characterized by weakness and fatigability of the muscle.
Myocardial infarction	An acute myocardial infarction is evidenced by any of the following: 1. A rise and fall of cardiac biomarkers (preferably troponin) with at least one of the values in the abnormal range (CK ≥ 5x ULN) together with at least one of the following manifestations of myocardial ischemia: a. Ischemic symptoms. b. ECG changes indicative of new ischemia (new ST-T changes, new left bundle branch block, or loss of R wave voltage). c. Development of pathological Q waves in 2 or more contiguous leads in the ECG (or equivalent findings for true posterior MI). d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 2. Development of new pathological Q waves in 2 or more contiguous leads in the ECG, with or without symptoms. 3. Imaging evidence of a region with new loss of viable myocardium at rest in the absence of a nonischemic cause. This can be manifest as:

Term	Definition
	a. Echocardiographic, CT, MR, ventriculographic or nuclear imaging evidence of left ventricular thinning or scarring and failure to contract appropriately (i.e., hypokinesis, akinesis, or dyskinesis); or, b. Fixed (non-reversible) perfusion defects on nuclear radioisotope imaging (e.g., MIBI, thallium).
Neuropsychiatric Complications (emotional changes)	A psychological or behavioral pattern generally associated with subjective distress or disability that occurs in an individual, and which is not a part of normal development or culture. Such a disorder may consist of a combination of affective, behavioral, cognitive and perceptual components.
Paresthesia	Abnormalities of sensation that are attributable to nerve damage or disorders.
Pneumonia	Lung infection documented by blood studies or chest x-ray, requiring treatment with antibiotics, inhalation therapy, intubation or suctioning.
Pulmonary Edema	An abnormal accumulation of fluid in the lungs requiring hospitalization or medical intervention to resolve.
Respiratory Failure	The need for ventilatory support for > 72 hours associated with an inability to wean from the respirator for any reason.
Sentinel Bleed or warning leak	Patient may report minor symptoms of headache, nausea, vomiting consistent with minor hemorrhage before a major rupture.
Slurred Speech	Slurred speech usually results from dysarthria, or difficulty with the pronunciation of words.
Subdural Empyema	Subdural empyema is a collection of purulent material between the dura mater and the arachnoid mater. The classic clinical syndrome is characterized by acute febrile illness that is punctuated by rapid progressive neurological deterioration, and, if left untreated, it will eventually lead to coma with fatal outcome.
Surgical wound infection	Surgical wound infections are classified as follows by the Centers for Disease Control and Prevention (CDC): Superficial incisional infection that only involves the skin and subcutaneous tissues. One of the following criteria has to be met: purulent discharge from the wound, isolated organism, at least one symptom of infection, and diagnosis by the surgeon. These infections account for more than 50% of all surgical infections. Deep incisional infections involve deeper tissues, including muscles and fascial planes. One of the following criteria has to be met: purulent discharge from the wound, dehiscence, or deliberate re-opening of deep incision by the surgeon after suspecting an infection, evidence of abscess formation, or other deep infection diagnoses by the surgeon. Organ/space infection may involve any organ apart from the incision site but must be related to the surgical procedure. One of the following criteria has to be met: purulent discharge from the drain placed in the organ, isolated organism from the organ, abscess, or other infection involving the organ.

Term	Definition
Syncope	Temporary loss of consciousness usually related to insufficient blood flow to the brain. It's also called fainting or "passing out."
Syndrome of inappropriate antidiuretic hormone secretion, dilutional hyponatremia (SIADH)	A disorder of impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH)
Tachypnea	Increase in respiratory rate >20 breaths per minute.
Tension pneumocephalus	Tension pneumocephalus is a rare but potentially life-threatening complication that occurs when a buildup of pressure within subdural air collections compresses the brain. The CT appearances of tension pneumocephalus include the "peaking" sign, in which subdural air collections compress the frontal lobes, and the "Mount Fuji" sign, in which compression and separation of the frontal lobes result in widening of the interhemispheric space.
Tremor	An involuntary, rhythmic muscle contraction leading to shaking movements in one or more parts of the body. Tremor may be intermittent (occurring at separate times, with breaks) or constant. It can occur sporadically (on its own) or happen as a result of another disorder.

UTI	Criteria for symptomatic UTI
	
	Non-catheterized:
	
	Minimum criteria include 1 of the following:
	
	• Acute dysuria or acute pain, swelling or tenderness of testes, epididymis or prostate
	
	OR
	
	• Fever (≥38°C or increase of at least 1.1°C above baseline), rigors or leukocytosis and at least 1 of the following symptoms (see below)
	
	OR
	
	• At least 2 of the following symptoms:
	  o New or increased frequency
	  o New or increased urgency
	  o New or increased incontinence
	  o Suprapubic pain
	  o Acute flank pain or tenderness
	  o Gross hematuria
	
	Catheterized: Minimum criteria include no alternative diagnosis AND 1 of the following:
	
	• Fever (≥38°C or 1.1°C above baseline), rigors or new-onset hypotension
	
	• Leukocytosis and either an acute change in mental status or acute functional decline

Term	Definition
	• New-onset flank or suprapubic pain or tenderness • Purulent discharge from catheter site • Acute pain, swelling or tenderness of testes, epididymis or prostate
Vasovagal episode	Type of syncope resulting from a failure in autoregulation of blood pressure, and ultimately, in cerebral perfusion pressure resulting in transient loss of consciousness.
Vertigo	A sensation of motion or spinning when not moving.
Ventriculomegaly	The fluid filled lateral ventricle of the brain are too large.

19.Version History

Version	Summary of Changes	Author(s)/Title
A	Not Applicable, New Document	Maunil Desai, Medical Writer
B	See table below "Changes in Rev B".	Maunil Desai, Medical Writer

Changes in Rev B

Sections Affected	Change in the CIP	Justification of Changes
All	Minor updates to language and formatting.	To maintain consistent and uniform language throughout the CIP
All	Name of the study changed to "ELEVATE".	Study update
All	The Pipeline™ Vantage Device replaced with the Pipeline™ Shield Device.	Study update
All	Clarified that "IIb/IIIa inhibitor" are "Glycoprotein IIb/IIIa inhibitor".	Study clarification
All	"Trial" updated to "study" "Site staff", "clinical site staff", "research staff", "investigation site team" updated to "site study personnel" "Clinical Site", "Research site" updated to "investigational site" "Subject (or their LAR)" updated to "subject or subject's LAR" "Clinical team", "sponsor team", "study team" updated to "Sponsor study team" or "Sponsor" "Protocol" updated to "CIP" or "Clinical Investigation Plan" with respect to the current CIP "Schedule of Events" updated to "Visit and Assessment Schedule" for Table 9-1 "Electronic study database" updated to "study database"	Study clarification
Sections 6.3 and Sections 8 through 16	Content of certain sections and sub-sections re-ordered per new CIP Template. A new Section 8 was added per new Template and subsequent sections were re-numbered.	CIP Template update
Table of Contents	Changes based on re-ordering of sub-sections.	Formatting updates
2	Updated definitions for access site complications, aneurysm occlusion, attempted procedure, cerebral edema, cerebral infarction, delayed intra-cranial hemorrhage (ICH), device thrombosis, dome-to-neck ratio, excessive radiation complications, implant success, index procedure, institutional review board (IRB)/ethics committee (EC), intention to treat population, intra-cranial hemorrhage, hydrocephalus, investigator, neurological deficit, parent artery stenosis, stacking, stroke, target aneurysm retreatment, thromboembolic complications, time 0, treatment-related procedural complications, vascular complications.	Study updates and clarification
2	Added definitions for anesthesia related complications, aneurysm maximum diameter, legally authorized representative (LAR), Modified Intention to Treat Population (mITT), peri and post procedural intra-cranial hemorrhage (ICH) within 30-days, procedural screen failure, screen failure, target aneurysm recurrence, telescoping, unavoidable event, visual impairment.	Study updates and clarification
2	Removed definitions for aneurysm dome, device movement, extra-axial hemorrhage, ipsilateral visual loss, intra-procedural hemorrhage, intra-procedural distal thrombotic complication, intra-procedural local	Study updates and clarification

	thrombotic complication, recurrence, retreatment procedure, symptomatic hemorrhagic event, visual symptoms (ipsilateral).	
2, 14.1	Updated definition of Intention to Treat population.	Per FDA feedback
2, 14.1	Updated definition of Per-Protocol population. Added definition for Modified Intention to Treat population.	Study updates/clarification
3, 7.5	Minor language update to Indication under investigation.	Study update
3, 4.4, 5.1, 6, 14.3	Primary Objective(s) updated to match indication.	Study clarification
3, 4.4, 6.1, 6.2, 14.1, 14.2	Added "adaptive" to study description.	Study clarification
3, 5.1.2	Defined disabling stroke adjacent to Primary Safety Endpoint.	Study clarification
3, 5.1.2	Secondary endpoints: Added 2 new endpoints (#11. Incidence of neurological death or disabling stroke post-procedure through 365-day follow-up and #12. Incidence of complete angiographic occlusion without significant stenosis (≤ 50%), and no rebleeding or retreatment of the target aneurysm through 365-day follow-up post-procedure)	Study updates and clarification
3, 5.1.2	Secondary endpoints – modified language of all endpoints by adding "Incidence of" for clarity.	Study clarification
3, 5.1.2	Secondary endpoints – Endpoints #7 and #8 extended to 365 days from 180 days.	Study update
3, 5.1.2	Secondary endpoints - Defined "device deployment success" and "disabling stroke" adjacent to Secondary endpoints.	Study clarification
3, 6	Minor language updates in "sample size & study centers".	Study clarification
3, 9.3	Inclusion Criteria: #4: Added "prior to the planned index procedure" for clarity.	Study clarification
3, 9.4	Exclusion Criteria: Minor language updates in #1, #2, #4, #11, #16, #19.	Study clarification
3, 9.4	Exclusion Criteria: #3: Removed "(aneurysms arising at a terminus)" #5: Added "Orogastric tube"	Study update
3, 9.4	Exclusion Criteria: Added two new criteria #20 and #21 20. Presumed septic embolus, or suspicion of microbial superinfection. 21. Subject with active COVID-19 viral infection, confirmed by testing.	Study update
3, 10.1 (Table 10-1), 10.14, 10.15	Added mandatory COVID testing at baseline screening. Added non-mandatory COVID testing at prior to discharge timepoint, 30-, 90-, 180-, and 365-day visits and unscheduled visit. Added footnotes #10 and #17 for COVID testing.	Study update
3, 10.1 (Table 10-1)	At 365-day visit, DSA imaging made mandatory.	Per FDA feedback
3, 10.1 (Table 10-1)	Minor language updates to footnotes for clarity.	Study clarification
3, 10.1 (Table 10-1), 10.7.2, 10.8, 12.1	Clarified that adverse events (AEs) will be collected and evaluated from the point of "arterial puncture".	Study update
3	Language update to "Statistics" in synopsis.	Study clarification
3, 14.3, 14.5	Both the primary effectiveness endpoint and the primary safety endpoint will be assessed with a one-sided test using a type I error rate of 0.025.	Per FDA feedback
3, 14.2	Upper limit of the promising range for Conditional Power defined as "80%" instead of "90%".	Study update
4	Minor language updates for clarity	Study clarification

4.2.1.6	Updated patient numbers for the INSPIRE Registry.	Study clarification
4.2.2.1	Updated Primary Effectiveness Endpoints for SHIELD OUS study per the SHIELD CSR Rev B.	Study clarification
6, 14.5	Updated reason for expected higher number of screen failures, and minor language updates.	Study clarification
6.1, 6.2	Minor language updates.	Study clarification
6.3	This was Section 15.1 (Steering Committee) in Rev A. Section renamed as "Study Oversight" per new Template. Language modifications to the content.	Study clarification
7	Minor language update in addition to change of study device. "Contraindications" no longer included as not required by the new CIP Template.	Study clarification
8.1	This was Section 15.2 in Rev A. Language modifications to "Investigational Site Selection".	Study clarification
8.2	New section "Study Site Activation" added.	Study update
8.3	This was Section 15.5 (Site Training) in Rev A. Section renamed as "Site Study Personnel Training". Language modifications to the content.	Study clarification
9.2	This was Section 8.2 in Rev A. Added or modified definitions of Pre-screen Failure and Procedural Screen Failure.	Study update
10 (Figure 10-1)	This was Section 9 in Rev A. Updated definition of Screen Failure and Procedural Screen Failure and device change. Removed "DSA imaging" from "Arterial Puncture" box.	Language consistency with rest of CIP
10.2	Section added per Template.	CIP Template update
10.3	Section added per Template.	CIP Template update
10.4	This text was under Section 9.2 in Rev A. Modified language.	CIP Template update
10.5	This text was under Section 9.2 in Rev A. Added COVID testing.	Study update
10.6	This text was under Section 9.3 in Rev A.	Study clarification
10.7	This text was under Section 9.4 in Rev A. Modified language for Subject Consent and added definition of Legally Authorized Representative (LAR).	Study update
10.8	This text was under Section 9.5 in Rev A. Added "Orogastric tube".	Study update
10.8.2	This text was under Section 9.5.2 in Rev A. Modified language in "Pre-Procedural Imaging".	Study clarification
10.9	This text was under Section 9.6 in Rev A. Clarified that "Primary interventionalist" is "implanting Investigator".	Study clarification
10.9.2	This text was under Section 9.6.2 in Rev A. Removed "device deployment success" from parameters determined by Core Lab.	Study update
10.9.3	This text was under Section 9.6.3 in Rev A. Clarified usage of multiple devices and added "telescoping".	Study clarification/update
10.9.4	This text was under Section 9.6.4 in Rev A. Usage of Ancillary Devices updated to match device change.	Study update
10.9.6	This text was under Section 9.6.6 in Rev A. Modified language in "No Treatment of an Eligible Subject with the Pipeline™ Shield Device (Unsuccessful Implant Procedure)".	Study clarification
10.10	This text was under Section 9.7 in Rev A. Modified language in "Medical Management Pre and Post Device Implant".	Study clarification
10.11.4	Moved "Aneurysm Occlusion Assessment" from Section 12.3 in Rev A.	Sub-section reordered

10.13	This text was under Section 9.10 in Rev A. Clarified "retreatment" based on definition in Section 2.	Study clarification
10.14	This text was under Section 9.11 in Rev A. Added "telephone" and "tele-video" visits.	Study update per COVID guidance
10.14.5	This text was under Section 9.16.4 in Rev A. Language modifications to "Missed Visits".	Study clarification
10.15	This text was under Section 9.11.5 in Rev A. Language modifications to "Unscheduled Visit".	Study clarification
10.16	This text was under Section 9.14 in Rev A. Language modifications to "Recording Data".	Study clarification
10.17	This text was under Section 9.15 in Rev A Language modifications to "Deviation Handling".	Study clarification
10.18	This text was under Section 9.16 in Rev A. Language modifications to "Subject Exit, Withdrawal or Discontinuation".	Study clarification
10.18.2	This text was under Section 9.16.1 in Rev A. Language modifications to "Withdrawal by Subject".	Study clarification
10.18.3	This text was under Section 9.16.2 in Rev A. Language modifications to "Investigator Withdraws Subject".	Study clarification
10.18.4	New sub-section "Sponsor Request to Withdraw Subject" added.	Study clarification
11.1	This text was under Section 10.1 in Rev A. Added "hemoptysis" to "Potential risk".	Per FDA feedback
11.1	This text was under Section 10.1 in Rev A. Added reference to RMW and IFU and language modification to terms under "Potential risk".	Study clarification
11.2	This text was under Section 10.2 in Rev A. Section heading renamed from "Risk Mitigations" to "Risk Minimization" per new Template.	CIP Template update
11.4	This text was under Section 10.4 in Rev A. Language modifications to text describing risk due to radiation.	Study clarification
12	This text was under Section 11 in Rev A. Language modifications to the text.	Study clarification
12.1	This text was under Section 11.1 in Rev A. 1. Updated definitions of AE, ADE, SAE, SADE, USADE per ISO 14155:2020 2. Updated definitions of UADE per 21 CFR 812.3 (s) 3. Scale for Event Severity specified as "National Cancer Institute (NCI) Adverse Event Severity Grading Scale – Common Terminology Criteria for Adverse Events (CTCAE)". 4. Updated language for "Causality Assessment of Events". 5. "Unavoidable Adverse Event" updated to "Unavoidable Event"	Study clarification
12.2	This text was under Section 11.2 in Rev A. Updated definition of Device Deficiency per ISO 14155:2020	Study clarification
12.3	This text was under Section 11.3 in Rev A. Language modification to "Reporting of Adverse Events". Updated SAE email hotline to "dl.ELEVATESAEhotline@medtronic.com".	Study update
12.4	New section "Processing Updates and Resolution" added.	Study update
12.5	New section "Subject Death" added.	Study update
12.6	New section "Product Complaint Reporting" added.	Study update
13	This text was under Section 12 in Rev A. Clarified information on CEC, PSC, Imaging Core Lab and Data Monitoring Committee.	Study clarification

14.1	This text was under Section 13.1 in Rev A. Analysis set definitions 1. Update ITT definition 2. Remove ICA definition 3. Include mITT definition 4. Update PP definition	Study clarification
14.2	This text was under Section 13.3 in Rev A. Now under "Interim Assessment for Sample Size Re-Estimation". 1. Change "interim analysis" to "interim assessment" 2. Removed statement about stopping for futility. 3. The lower threshold of the promising zone for conditional power is changed from 39% to 30%.	Study update
14.2.1	This text was under Section 13.8 in Rev A. Additional sub-section heading "Stopping the Trial Based on Interim Safety Data" removed.	Study clarification
14.3	This text was under Section 13.2 in Rev A. 1. Language modification to description of "Primary Endpoints". 2. The block of text beginning with the sentence, "The target sample size for the composite effectiveness endpoint is 100 patients." through the sentence, "If the conditional power is >39%, the independent Data Monitoring Committee (DMC) can re-estimate the sample size to ensure adequate power for the final analysis." removed. 3. Two lines of SAS syntax are removed. This level of detail can go in SAP.	Study clarification
14.4	This section includes text that was previously in section 13.5. Two changes: 1. Secondary endpoints removed from this section and cross-reference added to Section 5.1.2. 2. The detailed methods for summarization of the secondary endpoints will be included in the Statistical Analysis Plan.	Study clarification
14.5	This was Section 13.2 in Rev A. Justification for sample size and thresholds: 1. The paragraph comprising 13.2.1.1 (Justification for sample size) is moved to the beginning of the Sample Size Determination section (Section 14.5). This paragraph clearly states the overall sample size specified for the study. 2. The heading for this subsection is removed. 3. The hypothesis test statements are deleted as they are already stated in the primary endpoints section. Minor changes from Rev A to "Justification for safety endpoint threshold" text include the following: 4. Change the all caps "AND" to lower case 5. Remove the statement of the hypothesis test for the primary safety endpoint. This is stated above in the primary endpoints section. Minor changes from Rev A to "Justification for effectiveness endpoint threshold" text include the following: 6. Change the all caps "AND" to lower case 7. Remove the statement of the hypothesis test for the primary effectiveness endpoint. This is stated above in the primary endpoints section.	Study clarification
14.6	This was Section 13.4 in Rev A.	Study clarification

	Language modification to description of "Missing data and Imputation methods".	
14.7	This was Section 13.6 in Rev A. Updates to "Justification of Pooling".	Per FDA feedback
14.8	This was Section 13.7 in Rev A. Updates to "Subgroup Analysis".	Study clarification
15.1	This was Section 14.1 in Rev A. Language modifications to "Statement(s) of Compliance".	Study clarification
15.1.1	This was Section 14.1.1 in Rev A. Language modifications to "Sponsor Compliance".	Study clarification
15.1.2	This was Section 14.1.2 in Rev A. Language modifications to "Investigator Compliance".	Study clarification
15.2	This was Section 14.2 in Rev A. Language modifications to "Institutional Review Boards/Ethics Committee".	Study clarification
16.1	This was Section 15.3 in Rev A. Language modifications to "Monitoring".	Study clarification
16.2	This was Section 15.6 in Rev A. Language modifications to "Data Management".	Study clarification
16.3	This was Section 15.4 in Rev A. Language modifications to "Direct Access to Source Data/Documents".	Study clarification
16.4	This was Section 15.7 in Rev A. Section heading changed from "Onsite Audits" to "Sponsor Audits & Regulatory Inspections". Language modifications to "Confidentiality".	Study clarification
16.5	This was Section 15.8 in Rev A. Language modifications to "Confidentiality".	Study clarification
16.6	This was Section 15.9 in Rev A. Language modifications to "Liability".	Study clarification
16.7	This was Section 15.10 in Rev A. Language modifications to "CIP Amendments".	Study clarification
16.8	This was Section 15.11 in Rev A. Language modifications to "Record Retention".	Study clarification
16.9	This was Section 15.12 in Rev A. Language modifications to "Publication and Use of Information".	Study clarification
16.10	This was Section 15.13 in Rev A. Language modifications to "Suspension or Early Termination".	Study clarification

C	See table below "Changes in Rev C".	Maunil Desai, Medical Writer

Changes in Rev C

Sections Affected	Change in the CIP	Justification of Changes
All	Minor updates to language and formatting.	To maintain consistent and uniform language throughout the CIP
2	Updated definitions for Dome-to-Neck Ratio, Glasgow Coma Scale, Parent Artery Stenosis and Stroke.	Study updates and clarification
3, 5.1.2	Modified secondary endpoint #4 to include "or neurological death" and added definition of "major stroke" as a footnote.	Study update
3, 6	Language correction in "sample size & study centers".	Study clarification
3, 9.4	Exclusion Criteria: Language update to #3.	Study clarification

3, 10.1 (Table 10-1), 10.5	At baseline assessment, added clarity about COVID-19 testing and removed the requirement of "NIHSS to be carried out by a delegated qualified site study personnel".	Study clarification
3, 10.1 (Table 10-1)	Modified footnote #14 to clarify that NIHSS will be performed at "24" hours to align with Section 2. Added the following footnote #18 for clarity: "Subject is required to take CIP specified medication for a minimum of 180 days." Removed the requirement for review of CIP Specified Medication at 365 Day Visit and Unscheduled Visit.	Study clarification
3	Language update to "Statistics" in synopsis.	Study clarification
8.3	Minor language modifications to the content.	Study clarification
10.9.4	Added "balloon guide catheters".	Per FDA feedback
10.10.1	Minor language modifications to the content.	Study clarification
10.10.3.1	Added black box warning for Prasugrel (Effient).	Per FDA feedback
10.11.3, 13.3	Removed requirement of Physician Screening Committee approval for staged procedure(s).	Study clarification
10.14.4, 10.15	Clarified that "CIP Specified Medication" will be reviewed at 365 Day Visit and Unscheduled Visit "if subject is still on antiplatelet therapy".	Study clarification
11.1	Clarified "Potential risks".	Study clarification
12.1.9	"Unlikely" removed as a category from "Causality Assessment of Events".	Study clarification
14	Language modifications to the content.	Study clarification
14.9	Modified section on "Subgroup Analysis".	Per FDA feedback
16.2.1	Removed repeated text in "Data Quality Assurance" section.	Study clarification

D	See table below "Changes in Rev D".	Maunil Desai, Medical Writer

Changes in Rev D

Sections Affected	Change in the CIP	Justification of Changes
All	Changes based on re-ordering of sections since Section 2 Glossary was moved to Section 16.	Document update
All	Minor updates to language and formatting.	To maintain consistent and uniform language throughout the CIP
Cover page, Synopsis, 11, 14.1, 16	Addition of Local Sponsor – Canada and Health Canada specific requirements including ethics committee.	Addition of investigational sites in Canada
2, 6	Updated "Product Status" in the Synopsis. Added PMA number "P100018/S026" in Section 6.1 and updated Section 6.3.2 to reflect current status of Pipeline™ Shield Device. "Packaging" and "Product Use" sub-sections removed. Updated "Product Labeling and Indication for Use" and "Product Accountability" sub-sections to reflect current status of Pipeline™ Shield Device.	Change of status of study device
2, 5	Updated total number of sites and sites in the U.S. to 45 and 40, respectively.	Study update
2, 8.4	Exclusion Criteria: #13: Clarified that "known hypersensitivity" to ticagrelor or aspirin is an exclusion criterion, to match drug IFU. #19: Clarified exclusion criterion pertaining to subject participation in another trial during the duration of the study.	Study clarification

2, 8.4	Exclusion Criteria: #22: New exclusion criterion added – "Subject in whom a pre-existing stent is in place in the parent artery at the target aneurysm location".	New exclusion criterion per the investigational IFU.
2, 6.5, 9.9, 10.1, 11.6	Added "investigational" for the Pipeline™ Shield Device IFU specific to ELEVATE study to differentiate from commercially available IFU.	Change of status of study device
2, 9.1, 9.11.2, 9.14.3	Added a new assessment, "Clinical Vignette", in the "Visit and Assessment Schedule", "Prior to Discharge", and "180 Day Visit". Added associated footnote #19 in the "Visit and Assessment Schedule".	Study update
2	Clarified that PRU test will be performed in aspirin non-responders, to match content in Section 9.10.3.1.	Study clarification
5.2	Added information about commercialization of Pipeline™ Flex Device and Pipeline™ Shield Device.	Change of status of study device
9.11.2	Clarified the general information that will be collected prior to discharge.	Study clarification
9.13	Clarified that retreatment occurring after discharge from the index hospitalization will be considered an "Unscheduled Visit".	Study clarification
11.1.7	Updated the table in the "Unavoidable Event" section.	Study clarification
11.3	The upper time limit for reporting all reportable SAEs, Device Deficiencies with SADE potential, UADEs, and USADEs by the investigator after first learning of the event changed from "24" to "72" hours.	Administrative update. Follows all regulations around AE reporting and does not impact patient safety
16	Removed definitions for access site complications, anesthesia related complications, bleeding complications per GUSTO, cerebral edema, cerebral infarction, contrast induced complications, delayed intra-cranial hemorrhage (ICH), device technical success, device thrombosis, excessive radiation complications, hydrocephalus, intra-cranial hemorrhage (ICH), neurological death, neurological deficit, parent artery stenosis, peri and post procedural intra-cranial hemorrhage (ICH) within 30-days, stroke, target aneurysm rebleeding, target aneurysm recurrence, target aneurysm retreatment procedure, thromboembolic complications, transient ischemic attack (TIA), treatment-related procedural complications, vascular complications, and visual impairment.	Document update
16	Added definition for use error.	Document update
18.2	Appendix II added to define and classify anticipated adverse events and adverse device effects associated with use of the study device and the study procedure(s).	Document update

E	See table below "Changes in Rev E".	Maunil Desai, Medical Writer

Changes in Rev E		
Sections Affected	**Change in the CIP**	**Justification of Changes**
2, 8.4	Exclusion Criteria: Modified #21 to state "Subject with a known active COVID-19 viral infection".	Study clarification.
2, 9.1, 9.11.2	Added mRS assessment under "Prior to discharge" and specified that mRS will be collected at discharge in new footnote #19 in the "Visit and Assessment Schedule" table.	Study update.
2, 9.1, 9.11.2, 9.14.3	Modified the footnote #18 applicable to "Clinical Vignette" in the "Visit and Assessment Schedule" table and the applicable footnote under "Prior to Discharge" and "180 Day Visit" to clarify that the cause of disability will be assessed for subjects with mRS ≥3.	Study clarification.

2, 9.1, 9.11.2, 9.14	Revised footnote #5 in the "Visit and Assessment Schedule" table, the footnote in the section "Prior to discharge" and "Follow-up Evaluation and Visits" section to remove the verbiage "at the investigational site".	Study clarification.
2, 9.1, 9.5	Footnotes #10 and #17 were combined and subsequent footnotes were renumbered in the "Visit and Assessment Schedule" table. COVID-19 test was specified to be per standard of care in the "Baseline assessment" section.	Study clarification.
2, 13, 16	Modified the definition of ITT population to "all subjects who were consented and in whom deployment of the Pipeline™ Shield Device was attempted (i.e., puncture at the arterial access site), independent of the procedure being completed successfully". Stated that "The ITT analysis set will be used to evaluate all safety and effectiveness endpoints." Removed mITT population from the CIP.	Per FDA feedback.
10.1	Added new anticipated adverse events and adverse device effects related to radial access: hematoma, inflammation, infection, necrosis, pain and tenderness, granuloma and hand dysfunction.	FDA Interactive Review request.
10.5	Added information from clinical literature regarding risks of transradial access.	To maintain consistency with the newly added potential complications related to the radial artery access.
18.2	Added definition of "Hand Dysfunction" to Appendix II.	To maintain consistency with the newly added potential complications related to the radial artery access.
All	Minor updates to language and formatting.	To maintain consistent and uniform language throughout the CIP.

F	See table below "Changes in Rev F".	Maunil Desai, Medical Writer

Changes in Rev F

Sections Affected	Change in the CIP	Justification of Changes
18.2	Added "pathological hand cold intolerance" to the definition of "Hand Dysfunction" in Appendix II.	FDA Interactive Review request.

G	See table below "Changes in Rev G".	Elena Zoubina, Medical Writer

Changes in Rev G

Sections Affected	Change in the CIP	Justification of Changes
Footer	Updated to Clinical Investigation Plan Template 056-F275 Rev E, no change to content was required	The CIP Template was updated
3.2.1.6	Updated INSPIRE Registry enrollment information	Updated with information as of March 1, 2022
6.1.2	Added reference of Canada Medical Device Approval Licenses (MDL) for Pipeline Shield and Pipeline Flex	References of MDL provided to Health Canada
6.4, 10.1	Added reference to the investigational IFU M031954DOC2	Investigational IFU M031954DOC2 will be used to support Canada Health Investigational Testing Authorization application.

6.6	Added product accountability for Canada investigational sites	Updated to align with Canada Health Investigational Testing Authorization application.
H	See table below "Changes in Rev H".	Elena Zoubina, Prin. Medical Writer

Changes in Rev H

Sections Affected	Change in the CIP	Justification of Changes
2, 3.3, 3.4, 4.1, 5, 6.4, 8.1, 8,3, 10.5, 13.6	Updated: Indication under investigation to "The Pipeline™ Flex Embolization Device with Shield Technology™ is indicated for the endovascular treatment of adults (22 years of age or older) with acutely ruptured wide-neck intradural aneurysms not amenable to surgical clipping and coiling alone.", Investigation Purpose to "To assess the safety and effectiveness of constructive treatment with the Pipeline™ Shield Device in adults with acutely ruptured wide-neck (neck ≥4mm or dome to neck ratio ≤1.5) intradural aneurysms not amenable to surgical clipping and coiling alone.", and Imaging Inclusion criteria #1 to "Subject has a previously untreated, wide neck (neck ≥4mm or dome to neck ratio ≤1.5), intradural, side-wall target aneurysm including a blister, fusiform, saccular or dissecting aneurysm that is not amenable to surgical clipping and coiling alone, as confirmed on conventional digital subtraction angiography (DSA).	To align with updated AHA/ASA Guideline for the Management of Patients With Aneurysmal SAH
9.9.5	Adjunctive device use statement changed to: "Adjunctive devices (e.g. coils) may be used during the index procedure in conjunction with the Pipeline™ Shield Device in order to protect the dome of the aneurysm and reduce the risk of re-rupture. The use of coils is not required and will be at the discretion of the treating physician.	To align with updated indication under investigation.
2, 3.4, 4, 5.2, 13	Revised primary safety endpoint replacing "disabling stroke" with "major stroke in the territory supplied by the treated artery". Revised primary safety and effectiveness endpoints to be assessed at 365-day follow-up post-procedure.	Per FDA Study Design Considerations #1 and #2.
2, 4.1.2	Revised secondary endpoints #11 and #12 as to be assessed at 180 days. Replaced "disabling stroke" with "major stroke" in secondary endpoint #11.	Due to changes in the primary endpoints
13.7	Revised definition of subjects to be considered as "missing" for the primary safety endpoint to "the disposition of subjects who do not present for 365-day follow up, and/or for whom no evidence is available regarding a major stroke in the territory supplied by the treated artery or neurological death will be treated as missing".	To align with changes in the primary safety endpoint
5.2	Updated study rationale.	To provide justification for the update to the indication under investigation, investigation purpose and inclusion criteria.
18.2	Updated definition of the term "Stroke": 1. Added "new" to the definition, to read as "A new focal neurological deficit of presumed vascular origin persisting ≥24 hours from symptom onset with or without neuro-imaging findings or other quantitative study that does not indicate a different etiology." 2. Added "Unknown" to the assessment of outcomes related to disability.	1. Clarification since all subjects will have a stroke at presentation (at baseline) documented on imaging. 2. All subjects present with a stroke, and the impact of the initial SAH isn't known until

		the 30d mRS assessment. Therefore, for strokes that occur during index hospitalization, the impact of the new stroke on the mRS can't be determined, therefore disabling nature of the stroke cannot be accurately assessed.
10.1	Updated reference to RMW to reflect a current RMW document number. Added associated risks of TRA: radial artery spasm, radial artery perforation, infection, necrosis, pain and tenderness, compartment syndrome, radial artery occlusion, hematoma or hemorrhage, sterile inflammation, granulomas, hand dysfunction, amputation, and pathological hand cold intolerance.	Updated reference to RMW - administrative change, Added associated risks of TRA per FDA request
9.9.4	The following statement was added: "When using a catheter labeled for femoral artery access exclusively or with access site unspecified, radial artery access should be used only when femoral artery access is not feasible."	Per FDA request.
18.2 Appendix II	Added definitions for Compartment syndrome and Sterile inflammation as related to access site complications	To provide definitions of risks added per FDA request
Header, Footer, Title page, Sections 2, 3, 5, 6, 8, 9, 12	• Updated to Clinical Investigation Plan Template 056-F275 Rev F • Added "Version Date" row to the title page • Separated "Sponsor" and "Local sponsor" • Moved "Pre-clinical Summary" from section 6 (Product Description) to Section 3 (Introduction) • Moved "Study Oversight" from Section 5 (Study Design) to Section 12 (External Committees) • Moved "Subject Enrollment" from Section 8.2 to Section 8.4 • Moved "Subject Consent" from Section 9.7 to Section 9.5 • Changed heading of Section 12 from "Data Review Committees" to "External Committees"	To align with Clinical Investigation Plan Template update