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Study Protocol Title: A Study of the Pipeline™ Vantage Embolization **D**e**V**ice with Shield Technology™ for Endov**A**scular Treatme**N**t of Wide-Ne**C**ked Intracranial An**E**urysms (ADVANCE)

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Clinical Investigation Plan (CIP)

Clinical Investigation Plan/Study Title	**A** Study of the Pipeline™ Vantage Embolization **D**e**V**ice with Shield Technology™ for Endov**A**scular Treatme**N**t of Wide-Ne**C**ked Intracranial An**E**urysms
Clinical Investigation Plan Identifier	COVSHLD0569
Study Product Name	Pipeline™ Vantage 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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Confidentiality Statement

1. Investigator Statement

(Attached Separately)

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2. Glossary

Term	Definition

Access Site Complications	Include complications of the study procedure(s) that arise from access site puncture and introduction of devices required to establish access to the intended vascular territory being treated. These include the following:
	• **Hematomas/Hemorrhage** – to be further subcategorized as
	  ○ **Localized**: Painful swelling with indurated tissue around the access site which is usually treated with manual compression and analgesia, OR
	  ○ **Retroperitoneal**: Clinical signs including hypotension, lower abdominal or flank pain with an acute drop in hematocrit or hemoglobin. A high puncture at the site of arterial access (typically along the inguinal ligament) may also be noted. Confirmed with a computed tomography (CT) scan of the abdomen. May require blood transfusion to maintain stable hematocrit, and an endovascular or surgical intervention to treat.
	• **Pseudoaneurysm (PSA) -** an arterial rupture of one or more layers of its walls, contained by overlaying fibromuscular tissue, which communicates with an artery by a neck or sinus. Clinically presents with pain at arterial access site with a pulsatile mass with or without an audible bruit, with a duplex ultrasound or Doppler evidence of extra-arterial flow
	• **Vessel Occlusion -** Pain, pallor, paresthesia or decreased movement in the respective limb. Clinical examination that may reveal a cold ischemic limb with absent pulses or decreased ankle-brachial index (ABI). Condition may require endovascular or surgical intervention.

	• **Arteriovenous Fistula (AVF) -** New femoral bruit, thrill, fresh hematoma or pain in the lower limbs on the following day after sheath removal confirmed by color Doppler ultrasonography demonstrating an AVF with continuous systolic and diastolic flow. • **Deep Vein Thrombosis (DVT) -** Lower limb pain and swelling shortly following the endovascular intervention, confirmed by venous ultrasonography of the lower limb. • **Local Neurogenic/Nerve Complications** - Hypoesthesia, dysesthesia and hyperalgesia of the thigh caused by compression of femoral or cutaneous nerves or as a result of hematoma from the femoral artery access site. • **Pain:** Pain reported by the subject-specific to access site
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. (ISO 14155:2011 3.1) Note 1: 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: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
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. (ISO 14155:2011 3.2) Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved.

	Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Aneurysm Dome	Maximum horizontal diameter of the aneurysm.
Aneurysm Neck	Opening of the aneurysm where it meets the parent vessel
Aneurysm Occlusion	According to the Raymond–Roy Scale[1]: • 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™ Vantage Embolization Device with Shield Technology™ was attempted i.e., successful puncture at the arterial access site.
Bleeding Complications per GUSTO	Bleeding complications shall be adjudicated using the GUSTO bleeding criteria which includes categorizing all bleeding events into the following categories: • **Severe or Life-threatening:** ○ Intracerebral hemorrhage ○ Resulting in substantial hemodynamic compromise requiring treatment • **Moderate:** ○ Requiring blood transfusion but not resulting in hemodynamic compromise • **Mild** ○ Bleeding that does not meet above criteria
Cerebral Infarction	Evidence of new ischemic changes (infarction) on imaging. Further characterized as:

	• **Asymptomatic:** no associated focal neurological deficit symptoms (i.e., Silent Infarctions) • **Symptomatic:** focal neurological deficit symptoms lasting less than 24 hours
Contrast Induced Complications	Complications arising due to the use of contrast agent used for imaging requirements during study procedure(s).
Delayed Intra-Cranial Hemorrhage (ICH)	Any intracranial hemorrhage occurring >30 days post-procedure
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. (ISO 14155:2011 3.15) Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.
Device Movement	Unintended Pipeline stent (braid) Movement (as observed/discerned on imaging) of the implanted device following deployment. Device movement will be further characterized by: **Timing:** • **Intra-procedural:** Observed during the study index procedure • **Post-procedural:** Observed at a follow-up time point **Type:** • **Foreshortening:** 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. • **Device Embolization into Aneurysm:** Herniation into the aneurysm

	Clinical Significance: • **Clinically Significant:** When device movement causes unintended opening of the aneurysm neck leading to incomplete occlusion or is a reason for retreatment of the aneurysm. • **Not Clinically Significant:** When device movement does not cause unintended opening of the aneurysm neck leading to incomplete occlusion nor is a reason for retreatment of the aneurysm.
Device Technical Success	Device level analysis providing the rate of successful study device implantations at the target site with the total number of devices attempted to be deployed.
Device Thrombosis	Post-procedural, de novo formation of flow limiting 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.
Dome-to-Neck Ratio	Aneurysm dome max diameter/aneurysm neck width
Enrollment	Point at which the subject signs the study authorized Informed Consent.
Excessive Radiation Complications	Any noted procedural complications that are presumed to result from excessive radiation exposure due to imaging modalities.
Index Procedure	The first intended procedure to implant the study device where a successful puncture at the arterial access site is completed.
Institutional Review Board/Research Ethics Board	Institutional Review Board (IRB) is an appropriately constituted group that has been formally designated

	to review and monitor biomedical research involving human subjects. The Research Ethics Board (REB) helps ensure that this research meets the highest ethical standards, and that the greatest protection is provided to participants who serve as research subjects.
Intention to Treat Population (ITT)	All subjects who were consented and in whom deployment of the Pipeline™ Vantage Embolization Device with Shield Technology™ was attempted (successful puncture at the arterial access site), independent of the procedure being completed successfully.
Intra-Cranial Hemorrhage	• **Intra-Cranial Hemorrhage:** Hemorrhage within the fixed vault of the cranium (skull). ICH will be further categorized as: ○ Intracerebral Hemorrhage: ▪ ***Intra-Parenchymal Hemorrhage (IPH):*** • Bleeding within the cerebral matter (brain parenchyma), not involving the ventricles. **Note:** Acute Ischemic Stroke with hemorrhagic transformations included in the IPH will be explained in comments. ▪ ***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):** ▪ Occurs when there is tearing of the bridging vein between the cerebral cortex and a draining venous sinus ○ **Epidural Hematoma (EDH):** ▪ A rapidly accumulating hematoma between the dura mater and the cranium

	○ **Carotid Cavernous Fistula (CCF):** A fistula formation within cavernous sinus or due to aneurysm perforation/rupture ▪ Acute (intraoperative) ▪ Delayed (any time post-index procedure) In the event that a single hemorrhage event results in bleeding in multiple locations, the most severe category or primary hemorrhage should be selected. 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 dual antiplatelet therapy (DAPT) risk ▪ Hemorrhagic due to other causes
Intraparenchymal Hemorrhage	Bleeding within the cerebral matter (brain parenchyma), not involving the ventricles.
Investigator	Individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions (ISO 14155:2011 3.24)
Neurological Deficit	Events other than Strokes/Neurological Death that cause a decline in the mRS of the subject during follow up. These will be characterized by: **Focal:** Along the distribution of a cranial nerve or territory supplied by a particular intracranial vessel that is related to Target Aneurysm outcome (Ipsilateral) or Non-Target Aneurysm outcome (Contralateral): ▪ Cranial Nerve Palsy

	▪ Visual Field Deficit/Visual Loss ▪ Localized Ipsilateral Headache ▪ NOS (not otherwise specified) **Generalized:** Due to disease process other than intra-cranial aneurysms ▪ Amyotropic Lateral Sclerosis ▪ Motor Neuron Disease (Multiple Sclerosis etc) ▪ Myasthenia Gravis ▪ Spondylosis ▪ Alcoholism ▪ Depression ▪ Intra-Cranial mass ▪ Arthritis ▪ Trauma ▪ Malaise ▪ NOS (not otherwise specific)
Ipsilateral Localized Headache	Localized headache with a presumed treated vascular territory origin, that is new or worsening from baseline.
Ipsilateral Visual Loss	Events that cause a decrease in visual acuity and result in transient or permanent visual loss due to the intracranial aneurysm or its treatment.
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 via online portal BlueCloud (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 trial and will have no other responsibilities or duties associated with the trial.
National Institute of Health Stroke Scale (NIHSS)	Tool to quantify neurological impairment caused by stroke
Neurological Death	Any subject death where the primary cause is identified as neurological.
Parent Artery Stenosis	Any visually assessed parent artery stenosis report of > 1% stenosis of the parent vessel in the region of device placement on follow-up imaging. Stenosis will be classified in the bellow quartiles: • 1-25% • >25%- ≤ 50 % • >50% - ≤ 75 % • >75-100 % Each Parent Artery Stenosis event will also be adjudicated 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.

Per-protocol (PP) population	Per-protocol population is ITT subjects excluding the following subjects: - Subjects with use of more than 1 treatment device other than Pipeline™ Vantage Embolization Device with Shield Technology™ (e.g., adjunctive coils) during index procedure - Subjects with failed implantation of study device at index procedure - Subjects assessed as mRS ≥3 at baseline by independent and certified assessors
Principal Investigator (PI)	Qualified person responsible for conducting the clinical investigation at an investigation site (ISO 14155:2011 3.33)
Procedure	The primary study procedure involving the placement of the Pipeline™ Vantage Embolization Device with Shield Technology™ at Day 0.
Procedural Technical Success	Procedural Technical Success is measured by the rate of successful implantation of the study device during the study index procedure at the target site regardless of the number of devices deployed and implanted at the target site.
Recurrence	Aneurysm achieving complete occlusion (Raymond Roy 1) followed by incomplete occlusion (Raymond Roy 2 or 3) at follow-up exam, as assessed by Core Lab
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011 3.36)
Serious Adverse Event (SAE)	An adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject, that either resulted in 1. A life-threatening illness or injury, or 2. A permanent impairment of a body structure or a body function, or

	3. In-subject or prolonged hospitalization, or 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) Led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011 3.37) Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE.
Stroke	Stroke is defined as a focal neurological deficit of presumed vascular origin persisting ≥24 hours from symptom onset and a neuro-imaging study 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, intracerebral hemorrhage, or cerebral infarction. • 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 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, 24 hours later and at the time of discharge from the hospital where applicable with date and time of assessment.* Stroke Etiology Will be noted as: • **Ischemic** (when the primary cause of the stroke is ischemic) • **Hemorrhagic:** Stroke occurring following an aneurysm rupture or rapidly progressing sub arachnoid or IPH. Stroke Outcome will be noted with respect to mRS (assessed at a minimum of 90 days post stroke event) at each yearly study follow-up (1 year, 2 year, 3 year).: o Disabling (mRS with poor functional outcome i.e. ≥3 points) o Non-Disabling (mRS with good functional outcome 0-2 points)
Successful puncture at the arterial access site	Successful placement of sheath into the arterial access site
Target Aneurysm Retreatment	Any retreatment of the target aneurysm after the primary study procedure implantation with the study device These events will be further categorized by: • **Planned**: Retreatment procedure that 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
Target Aneurysm Rupture	Any rupture of the target aneurysm (aneurysm treated during the study index procedure). This will be further characterized as:

	• **Intra-procedural** – occurring during the index procedure • **Post-Procedural-** occurring anytime post-index procedure
Thromboembolic Complications	Procedural complication due to clot (thrombus formation) during the procedure that is visualized on angiography, limits blood flow through the vessel under treatment and requires intervention or causes neuro-imaging changes (infarctions). Further categorization will be provided for those events that meet the definition of: • **Distal Thromboembolic Complication**: Thrombus (or part of) that has broken off from the territory where it formed (e.g. treated vascular territory) and traveled to a distal location (e.g. untreated vascular territory) presumed to have occurred during the study procedure. For each thromboembolic complication, the disposition of patient impact status will be provided in terms of: • **Symptomatic:** Resulting in focal neurological status decline (Stroke, Symptomatic Cerebral infarction, TIA) • **Asymptomatic**: Resulting in no focal neurological status decline and includes silent cerebral infarctions.
Transient Ischemic Attack (TIA)	Focal neurological deficit symptoms lasting ≤24 hours (transient) with no evidence of cerebral infarction on imaging.
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))
Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2011 3.42)
Vascular Complications	Includes complications of the procedure that result in vascular injury due to introduction of ancillary devices (access catheters, sheaths, microcatheters, study device). These include the following: • **Dissection**: Physical separation of intima that results in exposure of internal arterial wall layers (media and/or adventitia) to blood. • **Perforation**: A tear or hole placed in a vascular structure of small nature, results in blood loss, but may not be as severe as a great vessel tear • **Rupture:** Rupture created entirely through the arterial wall causing significant amount of blood loss. • **Vasospasm:** Vasoconstriction observed during study procedure access of the aneurysm or treatment with study device. The vascular complications will be further classified as: ○ Intra-Cranial: Observed within the cerebral vessels (cerebral vasospasms) ○ Extra Cranial: Observed in neck vessels eg. external carotid artery ○ Peripheral: observed in the peripheral arteries e.g. femoral, radial, aortic etc.
Visual Symptoms (Ipsilateral)	All visual symptoms that appear as either a worsening from baseline or are new events from baseline and are presumed to be related to the study treatment in the absence of evidence of cerebral ischemia and not qualifying for ipsilateral cranial nerve palsies or neurological deficits

	These will be categorized further in the following symptom classifications with one event denoted to a single symptom: • Blurred Vision • Scintillations (e.g., Flashes of Light) • Eye Floaters (temporary clumpy obstruction of vision) • Diplopia (double vision) • Retinal artery occlusion (evidence of retinal artery occlusion on funduscopic exam) • Visual disturbance, Not Otherwise Specified (NOS) In addition, where known a categorization of symptom frequency will be done into one of the followings: ○ **Transient:** Continuous symptoms resolving within the study period. ○ **Permanent:** Continuous symptoms persisting at the end of the study period. ○ **Intermittent:** Non-continuous symptoms appearing and disappearing within the study period.

3. Synopsis

Title	**A** Study of the Pipeline™ Vantage Embolization **D**e**V**ice with Shield Technology™ for Endov**A**scular Treatme**N**t of Wide-Ne**C**ked Intracranial An**E**urysms
Clinical Study Type	Investigation Device Exemption (IDE) Study (Interventional)
Product Name	Pipeline™ Device Family with Shield Technology™ (referred to as Pipeline™ Vantage Embolization Device with Shield Technology™ in this CIP)
Sponsor	Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic)
Indication under Investigation	The Pipeline™ Vantage Embolization Device with Shield Technology™ is intended for endovascular treatment of adults (22 years of age or older) with wide-necked intracranial aneurysms located in the internal carotid artery (up to the terminus).
Investigation Purpose	The investigation purpose is to assess the safety and effectiveness of the Pipeline™ Vantage Embolization Device with Shield Technology™ in the treatment of intracranial aneurysms within the intended indication for use.
Product Status	Pipeline™ Vantage Embolization Device with Shield Technology™, investigational product in U.S.
Primary Objective	The primary objective of the study is to assess the safety and effectiveness of the Pipeline™ Vantage Embolization Device with Shield Technology™ in the treatment of intracranial aneurysms within the intended indication for use.
Primary Study Endpoints	**Primary Effectiveness Endpoint:** Incidence of complete aneurysm occlusion (Raymond Roy Scale Class 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure. **Primary Safety Endpoint:** Incidence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure.
Secondary Objective	The secondary objective of the study is to assess the safety and effectiveness of the Pipeline™ Vantage Embolization Device with Shield Technology™ in the treatment of intracranial aneurysms within the intended indication for use.
Secondary Endpoint(s)	**Effectiveness Outcome measures:** 1. Incidence of successful device implantation at the target site 2. Incidence of complete aneurysm occlusion (Raymond Roy Class 1) at 1- and 3-years post-procedure 3. Incidence of target aneurysm recurrence at 1- and 3-years post-procedure

	Safety Outcome measures: 1. Incidence of major stroke in the territory supplied by the treated artery or neurological death at 2- and 3-years post-procedure 2. Incidence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure 3. Incidence of delayed intraparenchymal hemorrhage >30 days post-procedure through 1-year post-procedure 4. Incidence of subjects with disabling strokes that have a mRS decline to a score of 3 or more (mRS ≥ 3) due to a stroke-related cause assessed at a minimum of 90 days post-stroke event at 1 year, 2 year, and 3 year post-procedure
Study Design	A prospective, global, multi-center, single-arm, IDE clinical study • Enrollment Duration: Approximately 1 year • Follow-up: 3 years • Total Study Duration: Approximately 4 years
Sample Size	Up to 140 subjects may be enrolled (consented) to ensure 100 evaluable subjects undergo attempted treatment with the Pipeline™ Vantage Embolization Device with Shield Technology™ at up to 30 sites, including up to 25 sites in the U.S. and up to 5 sites outside U.S. (OUS). The target sample size for this clinical investigation is 100 patients enrolled and treated and followed for safety events with the expectation of having follow-up imaging at 1-year post-procedure on a minimum of 80 patients.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** *Imaging Criteria (Core Lab Assessed)* 1. Subject has a target intracranial aneurysm located in the internal carotid artery (up to the terminus). 2. Subject has a target intracranial aneurysm with an aneurysm neck ≥4mm or a dome-to-neck ratio of < 2. 3. Subject has a target intracranial aneurysm that has a parent vessel with diameter 1.5–5.0 mm distal/proximal to the target intracranial aneurysm. *Clinical Criteria* 4. Subject (or subject's legally authorized representative) has provided written informed consent using the IRB/REB and Medtronic approved Informed Consent Form and agrees to comply with protocol requirements. HIPAA/data protection authorization has been

	provided and signed by the subject (or subject's legally authorized representative). 5. Age 22-80 years at the time of consent. 6. Life expectancy ≥3 years 7. Subject has a mRS ≤ 2 at baseline to be determined by a certified independent assessor at the site. 8. Subject has already been selected for endovascular treatment of the target aneurysm. 9. Subject's last recorded $P2Y_{12}$ reaction units (PRU) value is between ≥60 and ≤200 prior to study procedure. For OUS sites, a Thromboelastogram (TEG) test may be carried out instead of the PRU test (depending on PRU test availability). In cases where TEG test is carried out, the subject should have a pre-procedure therapeutic ADP% between >30% to <90%. 10. Subject has multiple increased risk factors for intracranial aneurysm rupture, including but not limited to, aneurysm morphology, smoking, hypertension, diabetes, age, prior and/or family history of rupture, and/or history of subarachnoid hemorrhage that may result in a benefit risk profile of endovascular treatment to outweigh the risks of intracranial aneurysm rupture during the subject's expected lifetime if left untreated. **Exclusion Criteria:** *Imaging Criteria (Core Lab Assessed)* 11. Subject has internal carotid artery bifurcation aneurysm. 12. Aneurysms that arise from the Posterior Communicating Artery (PComm). 13. The internal carotid artery aneurysms of the C7 segment will be excluded under the following conditions: a. Observed fetal posterior communicating artery (PComm) (A PComm of fetal origin is defined as a small, hypoplastic, or absent P1 segment of the posterior cerebral artery (PCA) with the PComm artery supplying a majority of blood flow to the P2 and higher order segments of the PCA) b. PComm overlapping with the aneurysm neck c. PComm branch arising from the dome of the aneurysm 14. Subject has aneurysm arising from internal carotid artery but is primarily fed by posterior circulation (i.e., retrograde flow from the basilar artery) as confirmed by DSA *Clinical Criteria*

	15. Subject requires treatment of another aneurysm (with another treatment modality) within the affected territory of the target aneurysm during the study period. 16. Subject has received an intracranial implant (e.g. coils) in the area of the target intracranial aneurysm within the past 6 months prior to the study procedure. 17. Subject has had a SAH and/or target aneurysm rupture in the past 30 days prior to the study procedure. 18. Subject has undergone a surgery including endovascular procedures in the last 30 days prior to the study procedure. 19. Vessel characteristics (e.g. severe tortuosity, stenosis, morphology) that preclude safe endovascular access to the aneurysm to allow for necessary access to treat with the study device. 20. 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, re-treatment, or device movement. 21. Subject has active vasospasm, malignant brain tumor or vascular malformation (e.g. arteriovascular malformation). 22. History of major bleeding disorder (based on coagulation profile and platelet count) and/or subject presents with signs of active bleeding. 23. Subject requires adjunctive device use (e.g. coils) during the index procedure. 24. Subject has extradural target aneurysm <12mm which is not symptomatic or not exhibiting aneurysm growth (exception: unless it is a fusiform aneurysm <12 mm i.e., asymptomatic extradural fusiform aneurysms <12 mm can be included). 25. Any known contraindication to treatment with the Pipeline™ Vantage Embolization Device with Shield Technology™, or use of antiplatelet therapy including: a. Active bacterial infection b. Contraindication to DAPT agents 26. Pre-existing stent is in place in the parent artery at the target intracranial aneurysm location 27. Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction. 28. The Investigator determines that the health of the subject or the validity of the study outcomes (e.g., high risk of neurologic events, conditions that may increase the chance of stroke) may be compromised by the subject's enrollment.

	29. Subject is pregnant or wishes to become pregnant during the first year of study participation. 30. 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. 31. Subject with known allergy to platinum or cobalt chromium alloy (including the major elements platinum, cobalt, chromium, nickel or molybdenum). 32. History of previous acute ischemic stroke 33. Subject is unable to undergo DSA or CTA imaging at follow-up.
Study Procedures and Assessments	**Treatment/Follow-up:** The study will consist of the following study visits: • Baseline • Pre-Procedure • Post-Procedure • Discharge exam • 30-day follow-up • 180-day follow-up • 1-year follow-up • 2-year follow-up • 3-year follow-up Eligible subjects will be treated with the Pipeline™ Vantage Embolization Device with Shield Technology™ per the Instructions For Use (IFU). All subjects will receive DAPT pre- and post-procedure as described in the protocol. A schedule of assessments to be performed at each study visit is listed in the table below:

Visits		Baseline	Procedure		Discharge exam	Follow-up					
			Pre- (Day 0)	Post- (Day 0)	Day 1-7	30-day	180-day	1-year	2-year	3-year	Un-scheduled
Assessments	Time Window	-7 to -30 days	Day 0	Day 0	1-7 days	±7 days	±30 days	± 56 days	± 56 days	± 56 days	
Assess Inclusion/Exclusion		X	X								
Informed Consent		X									
Demographics		X									
Medical History		X									
Risk Factors		X[1]									
Pregnancy Test			X[6]					X[6]	X[6]	X[6]	
WBC		X[10]									
Platelet count		X[10]									
Coagulation Profile (PT/aPTT)		X[10]									
Platelet Reactivity Testing			X[7]								
Protocol Specified Medications		X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X
DSA Imaging		X[2]	X[9]	X			X[4]	X	X[3]	X[3,4]	X[4]
MRA									X[3]	X[11]	X[4]
CTA							X[11]			X[11]	X[4]
Modified Rankin Scale (mRS)			X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5,8]
NIH Stroke Scale			X					X			X[8]
Neurological Exam		X			X	X	X	X	X	X	X
Assess Adverse Events		X[12]	X	X	X	X	X	X	X	X	X

[1] Risk factors to be assessed and collected for all subjects regardless of aneurysm size

[2] The baseline DSA, CTA OR MRA images must be taken no more than 90 calendar days prior to the procedure and core lab can use this for diagnostic or eligibility determination. Note that the pre-procedure exam for imaging would be with a DSA.

[3] If aneurysm is not occluded at 1 year or subsequent follow-up visits, DSA must be performed at 2- and 3- year follow-up. If child bearing potential woman becomes pregnant during the study, subject may obtain MRA without contrast instead of DSA.

[4] To be collected if conducted per standard of care

[5] mRS to be carried out by a certified independent assessor at the site. To become a certified independent assessor for mRS, the assessor should have passed a certification exam via online portal BlueCloud (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 trial and will have no other responsibilities or duties associated with the trial.

[6] Pregnancy test (serum or urine) only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test. At the 2- and 3- year follow-up, pregnancy test is only required for female subjects of childbearing potential that are undergoing DSA imaging.

[7] If PRU is found below 60 or above 200 on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is scheduled >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the PRU must be repeated, however, the baseline measurements may be repeated per standard of care at the treating hospital. For OUS sites, a TEG test may be carried out instead of the PRU test (depending on PRU test availability). In cases where TEG test is carried out, the subject should have a pre-procedure therapeutic ADP% between >30% to <90%. If ADP% is <30% or >90% on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is schedule >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the TEG measurements must be repeated but the other baseline measurements may be repeated per standard of care at the treating hospital. Note: treating physicians should also assess if ARU testing is required to assess aspirin responsiveness based on subject condition and response (per standard of care)

[8] For stroke events, mRS should be performed minimum of 90 days post event and NIHSS should be performed at the time of event and 24 hours after event.

[9] DSA at pre-procedure to be used for final aneurysm measurements can be done any time prior to the index procedure

[10] Can be done any time prior to the index procedure

[11] If DSA not collected per standard of care, subject must undergo CTA imaging. For follow-up images after the 1-year follow-up, under certain conditions, MRA imaging may be obtained instead of a DSA or CTA imaging e.g., subjects with iodine allergies, borderline renal function, pregnancy, or concerns over excessive radiation. The justification for using MRA over DSA or CTA should be captured in the case report form. Precaution: DSA or CTA imaging are preferred over MRA imaging due to the risk of reduced image quality (artifact) when attempting to visualize near or inside the implanted device with MRA imaging. Note that MRA should not be used for any follow-up imaging within 1-year

[12] Assess adverse events after informed consent is signed.

Statistics

Primary Hypothesis for Evaluating Study Success

The hypothesis for evaluating the primary safety endpoint will be evaluated according to the following 2 requirements:

Requirement 1: The incidence of primary safety events must be ≤7%, and

Requirement 2: The null hypothesis must be rejected in favor of the alternative:

H_o: Incidence at 1-year post-procedure of major stroke and/or neurological death is ≥ 14.0%

H_a: Incidence at 1-year post-procedure of major stroke and/or neurological death is < 14.0%

Given the primary safety endpoint reported in PMA P100018 (PUFs) was 5.6%, an incidence of ≤7% for the primary safety endpoint would be considered clinically acceptable within the confines of a study of this general size. If the incidence of primary safety events is ≤7% and the upper bound of the 1-sided 97.5% exact binomial confidence interval is <14%, the primary safety endpoint will have been met.

The primary effectiveness endpoint is the incidence of complete aneurysm occlusion (Raymond Roy Scale Class 1) without significant parent artery

stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure. The incidence will be summarized using counts and percentages; the 1-sided upper bound of the 97.5% confidence limit for the incidence will be evaluated relative to the a priori threshold of 50%. The hypothesis for evaluating the primary effectiveness endpoint is stated below:

H_o: Incidence at 1-year post-procedure of complete aneurysm occlusion without retreatment or significant parent artery stenosis is ≤ 50.0%

H_a: Incidence at 1-year post-procedure of complete aneurysm occlusion without retreatment or significant parent artery stenosis is > 50.0%

The pre-specified threshold of 50% for effectiveness endpoint is based on the effectiveness threshold of the recent PREMIER study with the Pipeline™ Device. This threshold must be exceeded at a certain magnitude to reject the null hypothesis and merely serves a statistical boundary for analysis. If the upper bound of the 1-sided 97.5% exact binomial confidence interval is >50%, the primary effectiveness endpoint will have been met.

Sample Size

The target sample size for this clinical investigation is 100 patients enrolled and treated and followed for safety events with the expectation of having digital imagery at 1-year post-procedure on a minimum of 80 patients. To calculate the sample size, simulations were prepared in SAS assuming an observed incidence in the ADVANCE IDE study of primary safety events ranging from 5.6% to 6.9%. With 100 patients and an observed incidence of safety event from 5.6% to 6.4%, the power exceeded 80%. Between the ranges of 6.5% to 6.9%, the power ranged from 79.8% to 74.7% for the primary safety endpoint and slightly below 80%. Although the power is less than 80 when the incidence of safety events was 6.5% or higher, the power was still considered adequate when contrasted against the actual upper bound of the 1-sided 97.5% exact binomial confidence interval. Specifically, if 7 of the 100 patients experience a primary safety event, the upper bound of the 1-sided 97.5% exact binomial confidence interval would be 13.89% and below the 14% threshold.

For primary effectiveness endpoint, the power was estimated for an observed rate between 65% to 80% considering sample sizes from 80 to 100 patients. With a type 1 error rate of 2.5%, 100 patients would have 82.8% power to reject the null hypothesis if the observed incidence of complete aneurysm occlusion without parent artery stenosis or retreatment was 65%. Under the same scenario with 80 patients, the power would be 83.5% if the observed incidence of complete aneurysm occlusion without parent artery stenosis was 67%. To

	ensure at least 95% power with 80 and 100 patients, the observed incidence of complete aneurysm occlusion without parent artery stenosis would need to be a minimum of 71% and 69%, respectively, which is relatively in-line with the previous results with the results from previous Pipeline studies. **Statistical Analysis** With the general exception of the tests comparing the response to an a priori threshold, all statistical tests will be 2-sided, performed at the 5% significance level. Baseline is defined as the last observation recorded prior to the study procedure. The primary effectiveness endpoint is the incidence of complete aneurysm occlusion (Raymond Roy Scale Class 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure; the 1-sided lower bound of the 97.5% confidence limit for the incidence will be evaluated relative to the a priori threshold of 50%. The primary presentation of the results for the ITT population will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. The primary safety endpoint is the incidence of major stroke in the territory supplied by the treated artery or neurological death recorded within 1 year of the study procedure. The incidence will be summarized using counts and percentages; the 1-sided upper bound of the 97.5% confidence limit for the incidence will be evaluated relative to the a priori threshold of 14%.

4. Introduction

4.1. Background

Intracranial aneurysms are common vascular abnormalities estimated to occur in 3-5% of the population.[2-6] Intracranial aneurysms can be classified according to size: small (<7 mm), medium (7-12mm), large (13-24 mm), and giant (≥25 mm). In terms of aneurysm morphology, the majority are saccular and are classified into either of two anatomical locations: side-wall or bifurcation aneurysms. The neck of the aneurysm for both of these aneurysm subtypes can be either narrow (<4 mm) or wide (≥4 mm).[7-9]

Most intracranial aneurysms are asymptomatic until they rupture, which can occur suddenly and without warning, leading to cerebral bleeding or subarachnoid hemorrhage (SAH). SAH is a devastating complication with a reported case-fatality rate of up to 45%, leaving nearly half of its survivors functionally incapacitated with less than 5% good outcomes.[1,10,11] Aneurysm characteristics including larger size, location (BasA bifurcation, vertebral/basilar artery, AcomA or PcomA), and morphology and shape (irregularity or lobulation, size ratio > 3 or aspect ratio > 1.6) have been shown to contribute to rupture risk.[12-16] Other aneurysm-related factors that may impact the risk of rupture include aneurysm de novo formation on serial imaging, contralateral steno-occlusive vessel disease, and aneurysm multiplicity. In addition to aneurysm-related factors, several patient-related factors, such as prior individual history or familial history of SAH, hypertension, cigarette smoking, drug use, alcohol abuse, cardiac conditions (including atrial fibrillation, cardiac arrhythmias, congestive heart failure, and myocardial infarction), psychiatric disorders, and epilepsy have been shown to contribute to rupture risk. Risk of aneurysm rupture has also been shown to be associated with aneurysm growth.[17-20] A meta-analysis conducted by Brinjinki et al. including 21 studies with 3,954 subjects examined the risk factors associated with aneurysm growth. The overall proportion of growing aneurysms was 3.0% per aneurysm-year, and aneurysm growth was associated with a rupture rate of 3.1% per year, compared with 0.1% per year for non-growing aneurysms ($p < 0.01$). Recent data suggests that aneurysmal growth is likely non-linear and occurs in episodes of instability and growth followed by periods of stability, which could add to the risk of rupture regardless of size.[21] Given the high mortality rate and poor prognosis associated with ruptured intracranial aneurysms, the goal of aneurysm therapy is to reduce the incidence of spontaneous rupture or to alleviate symptoms of mass effect related to aneurysm growth. The anatomic goals of intracranial aneurysm treatment are 1) to completely isolate the aneurysm sac from the circulation (i.e. complete occlusion) and, 2) to restore the morphologic integrity of the parent artery.[22]

In evaluating intracranial aneurysm treatment options, physicians commonly consider both surgical clipping and endovascular therapy, which differ in their ability to achieve complete occlusion. Surgical clipping of intracranial aneurysms is generally associated with good aneurysm occlusion, but high procedure-related mortality and morbidity rates. Endovascular treatment generally provides a safe and effective alternative to surgical treatment. Prospective controlled trials have demonstrated that endovascular coil embolization is associated with better outcomes compared to surgical clipping.[23-27]

In cases of wide-neck aneurysms, which are difficult to treat with coils alone, stent-assistance can be employed to prevent coil protrusion into the main vessel lumen. Stent-assisted coiling (SAC) uses conventional intracranial stents with low-metal-surface-area (high porosity), which are labeled as a humanitarian use device in the U.S.[28] SAC is used to treat wide-neck aneurysms by the scaffold they provide and can provide better initial occlusion rates while sparing the parent artery lumen and decrease likelihood of recanalization by altering the intra-aneurysmal hemodynamics.[28]

Although SAC of wide-necked aneurysms of various sizes represents a well-established and widely-applied treatment option, this treatment approach may be associated with sub-optimal long-term outcomes. In particular, SAC has shown diminished efficacy in the treatment of large and giant complex aneurysms, differing widely in terms of reported occlusion rates, ranging from 48-87.3%.[28-34] Furthermore, despite achieving complete occlusion, coil compaction over time may lead to aneurysm recurrence, necessitating retreatment. In a systematic review by Shapiro et al. on 39 published studies including 1,517 subjects with various-sized aneurysms treated by stent-assisted coiling, complete aneurysm occlusion was achieved in 61% of subjects at various follow-up times among studies.[35] In the same review, aneurysm recanalization was reported in 14% of subjects.[35] In other published literature on SAC for the treatment of aneurysms of various sizes, recanalization after treatment with coiling or SAC has been reported at rates between 16.8% and 59.1% for large/giant aneurysms[36-41] and between 6.2% and 16.9% for small/medium aneurysms.[42-47] Recurrence rates as high as 16.9% in small/medium aneurysms and 59.1%[48] in giant aneurysms after coiling alone, and as high as 10.5% for small/medium aneurysms after stent-assisted coiling have been reported in the literature.

Complications following SAC of large and giant complex aneurysms include neurological morbidity, such as ischemic and hemorrhagic events. [28-34] Reported morbidity rates ranged from 0-9.4% and a mortality rates from 0-4.1%.[28-34] Procedural and long-term outcomes across the studies evaluated indicate that the potential harms from coiling techniques include thromboembolic/stroke (1.4-8.7%) and hemorrhage (1.7-6%). In the aforementioned systematic review by Shapiro et al., 9% of cases were confounded by technical stent-related issues, including 4% failure of deployment.[35] The overall procedural complication rate was 19%, with a peri-procedural mortality of 2.1%. Thromboembolic issues were most prevalent at close to 10% while hemorrhagic complications occurred in 2.2% of cases–accounting for approximately 1% of all deaths. The authors concluded that next-generation endoluminal devices will likely expand the scope and effectiveness of endovascular aneurysm treatment.[35]

Flow-diverting devices represent a paradigm shift in the endovascular treatment philosophy for intracranial aneurysms and act in a two-fold manner:

(1) They divert flow away from the aneurysm sac, thereby inducing thrombosis within the sac and obviating the need for coil embolization; and

(2) They facilitate reconstruction of the parent vessel by providing a scaffold for endothelialization.

Pipeline™ Flex Embolization Device flow diverter is currently indicated in the US for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments. 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 (IAs) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm. The Pipeline™ Embolization Device and Pipeline™ Flex Embolization Device consist of the same device implant. The main difference lies in the delivery system. The Pipeline™ Flex Embolization Device improves on the Pipeline™ Embolization Device delivery system via incorporation of a resheathing mechanism and the replacement of the Pipeline™ Embolization Device protective coil with polytetrafluoroethylene (PTFE) sleeves. The resheathing mechanism allows physicians to reposition and redeploy the Pipeline™ Flex Embolization Device and the PTFE sleeves improve the physician's ability to release the implant.

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 0-13.9% associated morbidity and 0-6.9% mortality.[49-55] The PREMIER study (**Section 4.2.5**) on the Pipeline™ Embolization Device and the Pipeline™ Flex Embolization Device included 119 (84.4%, 119/141) small aneurysms (< 7 mm) and 22 (15.6%, 22/141) medium aneurysms (7-12 mm). Through 1-year follow-up, 81.9% (113/138) aneurysms had complete occlusion, none (0%; 0/138) had aneurysm recurrence and 2.9% (4/139) had aneurysm retreatment; delayed intracerebral hemorrhage >30 days through 1-year post-procedure occurred in 0.73% of subjects and the overall mortality rate was 0.7% (1/141). These rates are similar to or better than those for conventional intracranial aneurysm treatment of surgery or coiling.[38,56] Technical results of Pipeline™ Flex Embolization Device use show high procedural success (93-100%).[57-62] Additionally, the Pipeline™ Flex Embolization Device was associated with significant reductions in total procedure time, fluoroscopy time, patient radiation exposure, contrast usage, and rate of deployment failure compared with Pipeline™ Embolization Device.

Even though the Pipeline™ Embolization Device and Pipeline™ Flex Embolization 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 ischemic complications (including thromboembolic complications) and stenosis.[63,64] Thus, the next developmental modification to the Pipeline™ Device was adding the Shield Technology™ to the next generation device, Pipeline™ Flex Embolization Device with Shield Technology™. Shield Technology™ utilizes a phosphorylcholine (PC) surface modification to the existing implant combined with the Pipeline™ Flex Embolization Device delivery system. The Shield Technology™ surface modification applied to the implant is an inert, 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 PFED implant based on

bench data with human platelets and plasma.[65-68] In vitro assessment of PC-coated stainless steel demonstrated that it is resistant to fibrinogen adsorption, platelet activation, platelet adherence, and erythrocyte adherence.[69,70] Platelet adherence and thrombosis are also inhibited on PC-coated stents implanted in peripheral arteries of rabbits, pigs, dogs, and baboons.[69,71-73] The SHIELD OUS (**Section 4.2.7**) and PFLEX (**Section 4.2.8**) prospective, multi-centre, post-market studies were carried out to gather real-world safety and effectiveness data of the Pipeline™ Flex Embolization Device with Shield Technology™. 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™ Flex Embolization Device with Shield Technology™ 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™ Flex Embolization Device with Shield Technology™ is effective and safe for the endovascular treatment of intracranial aneurysms (**Section 4.2.7** and **4.2.8**).

The latest iteration of the Pipeline™ Embolization Device, the Pipeline™ Vantage Embolization Device with Shield Technology™ (herein after referred to as Pipeline™ Vantage), employs an enhanced version of the Pipeline™ Flex Embolization Device with Shield Technology™. Pipeline™ Vantage implant is a braided, multi-alloy, mesh cylinder woven from Drawn Filled Tubes (DFT) constructed from cobalt-chromium-nickel (MP35N LT) that is filled with a platinum core. The implant is modified with an inert surface treatment (**Shield Technology™**) that incorporates a durable, non-reactive material specifically designed to mimic human red blood cell membrane. The surface treatment is primarily composed of a phosphorylcholine polymer (Lipidure®-NH01). Design enhancements to the braided implant (**Section 7.1.1**) are intended to enhance radiopacity, delivery forces, distal, middle and proximal opening. The delivery system (**Section 7.1.1.4**) utilizes a single tapered core wire for improved one to one response, including a larger proximal portion for enhanced pushability. The newly designed Advanced Resheathing Mechanism (ARM) engages the pores of the braid to enable resheathing with enhanced reliability. Design enhancements to the delivery system are intended to enhance tactile feedback, delivery forces and include a low-profile delivery.

For pre-clinical application, 9 published pre-clinical studies analyzed thrombogenicity, endothelialization, stenosis, and aneurysm occlusion for Pipeline™ Flex Embolization Device with Shield Technology™.[74-82] Three of these studies[74,75,81] compared thrombogenicity of Pipeline™ Shield to other flow diverters such as Pipeline™ Embolization Device (PED),[75] Pipeline™ Flex,[74,81] SILK+,[74] P64,[81] Derivo®,[81] and Flow Redirection Endoluminal Device (FRED™)[74,75] in vitro under varied antiplatelet regiments. These studies reported that the Pipeline™ Shield device led to significantly lower thrombin generation,[74,81] platelet activation,[81] aggregation,[81] and deposition on device surface,[75,9] and significantly lower fibrin accumulation[75] than the other flow diverters studied, with or without antiplatelet therapy. These results provided clinically relevant evidence that the Shield Technology™ surface modification of endoluminal stents could be an effective method to mitigate thrombogenic complications associated with aneurysm

treatments. Further, 6 studies[76-80,82] compared the Pipeline™ Shield device to the other flow diverters such as PED,[76,77,79,82] Pipeline™ Flex,[78,80] and FRED™[82] using animal models. Under various single or dual antiplatelet therapy regimens, Pipeline™ Shield implantation was shown to be associated with less thrombus formation on the surface of the device,[77,80,82] especially post-angioplasty.[82] As compared to PED, in-stent stenosis was reduced in Pipeline™ Shield without DAPT[76] and was reported as 0% with DAPT,[76] and neointimal hyperplasia was reduced without reducing aneurysm occlusion.[79] At the same time, these studies demonstrated faster endothelium growth[80] with more evenly distributed concentric neointimal formation,[78] comparable neointimal volume (to other flow diverters),[78,80] and earlier healing response[78] after the Pipeline™ Shield device implantation. 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 PED and other flow diverters.

4.2. Clinical Experience with the Pipeline™ device

The clinical benefits achieved with the use of use of Pipeline™ Embolization Device have been consistently demonstrated in multiple clinical trials.[49,50,52-54,83-88] 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-neck aneurysms, or aneurysms with complex morphology).[50,54,55,89-91] Clinical outcomes from 8 key studies on the Pipeline™ Device (including, Pipeline™ Embolization Device, Pipeline™ Flex Device, and Pipeline™ Flex with Shield Technology) have been summarized below.

4.2.1. PITA: Pipeline for Intracranial treatment of Aneurysms

The PITA study was the first prospective multi-center trial 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 of 47 Pipeline™ device braids were placed successfully (97.9%). 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.

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

The PUFs study was a multi-center, prospective, single-arm trial to evaluate the safety and effectiveness of the Pipeline™ Embolization Device (PED) 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 PED. 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%–81.0%). At one year, 86.8% (79/91) of the target aneurysms were completely occluded. This rate increased to 95.2% (59/62) complete occlusion at five 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 six of the 107 subjects (5.6%; 95% posterior probability interval: 2.6%–11.7%). At five year follow-up, and the rate of major ipsilateral stroke or neurologic death remained 5.6%.[92]

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

The IntrePED study was a retrospective global post-market study of subjects treated with the PED at 17 centers worldwide.[85,93] 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% 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). Data from the IntrePED study report the safety of the PED in the treatment of various intracranial aneurysms in a real-world clinical setting.

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

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

Neurological morbidity was 6.8% (13/191) and the neurologic 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 PED treatment.

Aneurysm occlusion was assessed by an independent core lab according to the Scale of Roy at last visit for all subjects with imaging follow-up of at least 6 months. 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 PED use in the real world, confirmed that the PED 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.

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

PREMIER was the first prospective, multicenter trial to evaluate the use of the Pipeline™ device for the treatment of small and medium, unruptured aneurysms of the intracranial carotid and proximal vertebral artery. The study was conducted in 1 Canadian and 22 US 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. 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/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%; 0/138) had aneurysm recurrence and 2.9% (4/139) had aneurysm retreatment at the 1-year follow-up. 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 intracranial carotid and proximal vertebral artery.

4.2.6. 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 Clinical Events Committee and effectiveness endpoints measured by an independent core laboratory. INSPIRE was launched in December 2016; and up to July 2019 includes 600 patients with intracranial aneurysms treated with the Pipeline™ Flex or Pipeline™ Shield flow diverting devices. Patients were enrolled from 30 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.

4.2.7. 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 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 ICA (segments C1-C7) (76.0%, 155/204), MCA (7.8%, 16/204), Vertebral Artery (6.4%, 13/204), Anterior Communicating Artery (5.9%, 12/204), and 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 Study Protocol 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 4-1**.

Table 4-1. 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[1]) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure		
FAS# population (N=200)	71.67%	(64.95%,77.74%)
ICA†-FAS population (N=149)	75.30%	(67.58%,81.99%)
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-neck aneurysms are poor candidates for endovascular treatment with coils. Along with the possibility of coil protrusion into the parent vessel, there are reportedly high rates of aneurysm recurrence or recanalization after treatment.[7,94-96] Current evidence demonstrates that the Pipeline™ device meets the need for the treatment of wide-neck intracranial aneurysms and results in high complete occlusion rates, low recurrence rates and a favorable safety profile.

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

The primary objective of the Pipeline™ Flex Embolization Device with Shield Technology™ Clinical Study or PFLEX Study was to assess the outcomes of the 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 100.0% (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 4-2**.

Table 4-2. 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[1]) 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.

4.3. Purpose

A Study of the Pipeline™ Vantage Embolization Device with Shield Technology™ for Endovascular Treatment of Wide-Necked Intracranial Aneurysms (ADVANCE Study) is a prospective, global, multi-center, single-arm IDE study of the Pipeline™ Vantage device for the treatment of adults (22 years of age or older) with wide-necked intracranial aneurysms located in the internal carotid artery (ICA) (up to the terminus). The primary purpose of the ADVANCE Study is to assess the safety and effectiveness of the Pipeline™ Vantage device in the treatment of unruptured intracranial aneurysms within the intended indication for use. The safety of the Pipeline™ Vantage will be assessed through incidence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure. The effectiveness of the Pipeline™ Vantage will be assessed through incidence of complete aneurysm occlusion (Raymond Roy Scale Class 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure. Additional safety and effectiveness analyses will include incidence of major stroke in the territory supplied by the treated artery or neurological death at 2- and 3-years post-procedure, incidence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure, incidence of delayed intraparenchymal hemorrhage >30 days post-procedure through 1-year post-procedure, incidence of subjects with disabling strokes that have a mRS decline to a score of 3 or more (mRS ≥ 3) due to a stroke-related cause assessed at a minimum of 90 days post-stroke event at 1 year, 2 year, and 3 year post-procedure, incidence of successful device implantation at the target site, incidence of complete aneurysm occlusion (Raymond Roy Class 1) at 1- and 3-years post-procedure, incidence of target aneurysm recurrence at 1- and 3-years post-procedure.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this study is to assess the safety and effectiveness of the Pipeline™ Vantage Device in the treatment of intracranial aneurysms within the intended indication for use*.

*The Pipeline™ Vantage Embolization Device with Shield Technology™ is intended for endovascular treatment of adults (22 years of age or older) with wide-necked intracranial aneurysms located in the internal carotid artery (up to the terminus).

5.1.1.1. Primary Endpoints

5.1.1.1.1. Primary Effectiveness Endpoint

The following will be assessed for the primary effectiveness endpoint:

- Incidence of complete aneurysm occlusion (Raymond Roy Scale Class 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure.

Complete occlusion and parent artery stenosis will be adjudicated by the Imaging Core Laboratory. Retreatment will be assessed per site records.

5.1.1.1.2. Primary Safety Endpoint

The following will be assessed for the primary safety endpoint:

- Incidence of major stroke in the territory supplied by the treated artery or neurological death at 1-year post-procedure

This endpoint will be adjudicated by the independent Clinical Events Committee (CEC).

For the purposes of this study protocol, stroke is defined as a focal neurological deficit of presumed vascular origin persisting ≥24 hours from symptom onset and a neuro-imaging study 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, intracerebral hemorrhage, or cerebral infarction.
- 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 disorder such as leukemia or external events such as trauma.

Severity of stroke will be classified by the CEC as major or minor:

- 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.

Disability status of the Stroke events will be assessed based on mRS assessment conducted 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)

  The following assessments are required to be performed (if hospitalized at the primary investigative site) or source documents obtained (if hospitalized at an outside hospital) for All Stroke Events:

  - NIHSS at time of Stroke presentation to the hospital
  - NIHSS at 24 hrs from the Stroke presentation
  - mRS assessment at a minimum of 90 days post-Stroke event
  - Any Imaging / imaging report available during Stroke hospitalization

Neurological death is any death of a subject in which the primary cause of death is due to neurologic reasons.

The following documents are to be obtained for all events that lead to Death:

- Hospitalization Record (where available)
- Autopsy Report (where available)
- Death Certificate (where available)

A PI note describing the last subject contact with detail of any assessments to be provided where Death Certificate is not available.

5.1.2. Secondary Objective(s)

The secondary objective of this study is to assess the efficacy and safety of the Pipeline™ Vantage Device in the treatment of intracranial aneurysms within the intended indication for use.

5.1.2.1. Secondary Endpoint(s)

The following will be assessed for the effectiveness outcome measures:

1. Incidence of successful device implantation at the target site
2. Incidence of complete aneurysm occlusion (Raymond Roy Class 1) at 1- and 3-years post-procedure
3. Incidence of target aneurysm recurrence at 1- and 3-years post-procedure

For the purposes of this study protocol, successful device implantation will be presented in terms of Procedural Technical Success and Device Technical Success. Procedure technical success is measured by the rate of successful implantation of the study device during the study index procedure at the target site regardless of the number of devices deployed and implanted at the target site. Device technical success is measured by the rate of successful study device implantation at the target site with the total number of devices attempted to be deployed.

Successful device implantation and retreatment will be site reported. Aneurysm occlusion class, recurrence, and parent artery stenosis will be assessed by the independent Imaging Core Lab.

The following will be assessed for the secondary safety endpoints:

1. Incidence of major stroke in the territory supplied by the treated artery or neurological death at 2- and 3-years post-procedure
2. Incidence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure
3. Incidence of delayed intraparenchymal hemorrhage >30 days post-procedure through 1-year post-procedure
4. Incidence of subjects with disabling strokes that have a mRS decline to a score of 3 or more (mRS ≥ 3) due to a stroke-related cause assessed at a minimum of 90 days post-stroke event at 1 year, 2 year, and 3 year post-procedure

The events comprising the safety endpoints will be adjudicated by the independent CEC.

6. Study Design

The study is a prospective, global, multi-center, single-arm IDE clinical study evaluating the performance of the Pipeline™ Vantage Device. The Pipeline™ Vantage Device is investigational in the United States and Canada.

6.1. Duration

Subjects will actively participate for approximately 3 years. Study participation includes Baseline, Pre-Procedure, Post-Procedure, Discharge exam, and follow-up visits at 30-day, 180-day, 1-year, 2-year and 3-year. Enrollment will be approximately 1 year. The total study duration is expected to be approximately 4 years.

6.2. Rationale

The Pipeline™ Embolization Device has been commercialized in the US since 2011 for the endovascular treatment of adults with large (≥ 10-24 mm) or giant (≥ 25 mm) wide-necked intracranial aneurysms in the ICA from the petrous to the superior hypophyseal segments. Over time, additional long-term data has been generated which further confirms the safety and effectiveness of the Pipeline™ Embolization Device for this indication. Additionally, outside the US, the Pipeline™ Embolization Device has been approved and commercialized since 2008 for endovascular embolization of cerebral aneurysms.

The latest developmental modification to the Pipeline™ Embolization Device (PED) system is Pipeline™ Vantage Embolization Device with Shield Technology™. Pipeline™ Vantage utilizes the same phosphorylcholine (PC) surface treatment (**Shield Technology™**) as the Pipeline™ Flex Embolization Device with Shield Technology™. Additionally, the wire design and braid pattern are unchanged in Pipeline™ Vantage. However, there are some key enhancements in the Pipeline™ Vantage device. Pipeline™ Vantage implant has larger implant diameters and longer lengths, drawn filled tubes and decreased wire diameter as well as increased pore density (**Section 7.1.1**). These changes to the implant increase radiopacity, optimize deliverability and enhance the ability of the implant to open upon deployment. The Pipeline™ Vantage delivery system (**Section 7.1.1.4**) was designed to be compatible with 0.021" inner diameter micro catheters for select sizes and also includes a new Advanced Resheathing Mechanism, Corewire-based Delivery System and Corewire Subassembly for improved reliability. The Shield Technology™ surface treatment applied to the implant is an inert, 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 current bare metal Pipeline™ Embolization Device implant based on bench data with human platelets and plasma.

Objective evidence on the safety and effectiveness of the Pipeline™ Vantage Device is best collected by conducting a prospective study with standardized follow-up evaluations. The use of an independent core

lab is uncommon in studies evaluating intracranial aneurysms despite evidence showing site reported data underestimates unfavorable angiographic appearance.[97,98] Along with an independent core lab, the Pipeline™ Vantage Device trial will employ an independent Data Monitoring Committee (DMC) and an independent Clinical Events Committee (CEC) to assist in the oversight and analysis of the study data. Treatment with the Pipeline™ Vantage Device is expected to show high complete aneurysm occlusion rates and minimal safety events.

The patient population proposed for enrollment in the study includes patients with a wide-neck intracranial aneurysm located in the internal carotid artery (up to the carotid terminus). The justification for the patient population and the single-arm study design is provided below.

Small, Medium, Large, and Giant Wide-Necked Aneurysms

Pipeline™ Flex Embolization Device flow diverter is currently indicated in the US for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments. 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 widenecked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysm (IAs) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm. The device has shown high effectiveness and low complication rates for this indication.[84]

In addition to evaluating large and giant wide-neck aneurysms, the proposed study also aims to include wide-neck aneurysms measuring <10mm. There is a lack of consensus in the literature and guidelines on whether small and medium size aneurysms should be treated. The natural course of untreated aneurysms of specific size ranges has not been clearly identified.[99-103] Although several studies have reported a wide range of rupture rates over time for untreated small and medium size aneurysms of various locations; annual rupture rates for small and medium size aneurysms vary significantly up to a 20 fold difference (0.05% vs. 1.0%, annually).[99,102-106] This most likely can be explained by the fact that in addition to aneurysm size, the risk of aneurysm rupture is attributed to various other factors, including aneurysm morphology, location, previous subarachnoid hemorrhage, and subject characteristics.[100,105,107,108]

In the Small Unruptured Intracranial Aneurysm Verification (SUAVe) Study, patient age, aneurysm diameter ≥4 mm, hypertension, and aneurysm multiplicity were significant predictive factors for rupture of small aneurysms.[108] The average annual risk of rupture for small aneurysms (<5 mm) in the study was 0.54% overall, 0.34% for single aneurysms and 0.95% for multiple aneurysms (mean follow-up: 41 months).[108] Another study which followed the natural course of unruptured aneurysms with a mean size of 5.7 mm in 5720 patients reported a similar annual rupture rate to the SUAVe study at 0.95% (follow-up: 3 months to 8 years). The annual rupture rates from both studies, however, may be an underestimate

due to possible selection bias. Data from patients who underwent surgical intervention were censored and some of these patients may have been at an increased risk for rupture.[100,108]

Although the rupture rate for untreated unruptured small and medium aneurysms is low, it is also important to consider that the majority of unruptured intracranial aneurysms are small and medium in size. In the International Study of Unruptured Intracranial Aneurysms (ISUIA) study, out of 1692 untreated, 1917 surgically treated, and 451 endovascularly treated subjects, 85%, 78%, and 58% of the subjects' aneurysms were ≤12 mm in size, respectively. In a meta-analysis of 71 studies investigating the endovascular treatment of intracranial unruptured aneurysms, of the 2688 patients included, 75% of the patient's aneurysms' were < 10 mm in size. Furthermore, in recent randomized controlled trials in which bare metal coils were studied against alternative treatment options in hundreds of patients, both unruptured and ruptured aneurysms were included and the majority of patients treated had small and medium size aneurysms.[14,109-112]

Data for ruptured aneurysms also supports the treatment of small and medium aneurysms. Many of the aneurysms that rupture are small or medium in size. In the International Subarachnoid Aneurysm Trial (ISAT), a landmark trial on the treatment of 2143 ruptured intracranial aneurysms, 92% of the ruptured aneurysms were ≤ 10 mm.[27] Similarly, in the CLARITY study of ruptured aneurysms, 89.5% (700/782) of the subjects had an aneurysm ≤ 10 mm.[113] Treatment of a ruptured aneurysm is critical in order to stop the bleeding and attempt to reduce the risk of potentially devastating complications. Since a significant majority of ruptured aneurysms reported in the literature appear to be small and medium in size, these findings support the fact that these aneurysms pose a considerable risk and warrant careful consideration for treatment.[26,27,101,114]

Multiple publications demonstrate that these small and medium wide-necked aneurysms are commonly treated endovascularly with SAC.[115-122] Although initial occlusion rates are good, the primary limitation of SAC is the inability to provide sustained long-term aneurysm occlusion. Aneurysm recurrence rates of up to 16% have been reported in the literature after SAC treatment of small and medium IAs.[30,115,117,118,121,123,124] The presence of major aneurysm recurrence requires retreatment, which is evidenced by aneurysm retreatment rates of up to 10% for small and medium IAs.[119,121-126] Therefore, an alternative approach for obtaining sustained aneurysm occlusion, such as flow diversion, is needed for small and medium wide-necked intracranial aneurysms.

In the IntrePED trial, a post-market registry to evaluate the Pipeline™ Embolization Device in which all consecutive subjects treated with the Pipeline™ Embolization Device were required to be enrolled, more than half the aneurysms treated (473/896, 52.8%) were small (<10 mm).[85,93] Combined neurologic morbidity and mortality for small unruptured anterior circulation aneurysms was 3.5% (11/311) and 0.0% (0/24) for small unruptured posterior circulation aneurysms. When specifically evaluating small (<10 mm) aneurysms located in the ICA, the rate of neurologic morbidity in ruptured and unruptured aneurysms was 4.1% (12/291), neurologic mortality was 1.4% (4/291) and the combined rate of neurologic morbidity

and mortality for unruptured aneurysms was 3.4% (9/268). The overall IntrePED study results show that intracranial aneurysms measuring less than 10 mm are treated frequently and are associated with low complication rates.

Although there is some debate within the medical community regarding treatment of small and medium sized wide-neck aneurysms, it is clear from the literature that physicians worldwide treat a significant number small and medium aneurysms, both unruptured and ruptured. When deciding treatment approach, physicians take numerous factors into account in addition to aneurysm size, including age, aneurysm morphology, location, medical history and co-morbidities, previous SAH, and individual subject characteristics. After consideration of these factors, many times physicians conclude that the benefit of endovascular treatment outweighs the risk and subsequently treat these aneurysms. These cases demonstrate the need for endovascular treatment in a selected subject population and further, that these subjects may benefit from treatment with the Pipeline™ Vantage Device.

It is also important to note that subjects with unruptured or ruptured (>30 days since occurrence) small and medium aneurysms proposed for enrollment in the current trial are those who have already been identified by their physician as being appropriate for endovascular treatment of their aneurysm. Investigators and subjects will first make the collective determination regarding the appropriateness of endovascular treatment based on their clinical expertise and experience. This will be the same process and decision that physicians, in consultation with subjects are currently performing when determining whether to treat subjects with small and medium aneurysms using endovascular coils. Only after the decision has been made by the physician and subject to treat the aneurysm through endovascular means, will the potential for enrollment into the proposed study be considered.

The following inclusion criterion will be used as a treatment inclusion risk mitigation measure to ensure only those small aneurysm subjects who demonstrate an appropriate level of aneurysm rupture risk, will be enrolled into this study. “Subject has been already selected for endovascular treatment of the target aneurysm. If the target aneurysm measures ≤5mm, risk factors leading to the determination to treat the aneurysm must be identified.”

Internal Carotid Artery (up to the terminus)

Treatment with the Pipeline™ Flex Embolization Device is currently indicated in the U.S. for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments. 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 widenecked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysm (IAs) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm. The proposed study aims to include intracranial aneurysms in the ICA up to the terminus. The majority of aneurysms in the IntrePED study

were located in the ICA (684/906, 75.5%) and ranged in size from small to giant (360 small, 272 large and 45 giant aneurysms, respectively).[85,93] The combined neurologic morbidity and mortality rate for subjects with unruptured ICA aneurysms <10mm was 3.4% (9/268) and the combined neurologic morbidity and mortality rate for subjects with unruptured ICA aneurysms ≥10mm was 9.5% (27/285). These rates demonstrate that the Pipeline™ Vantage Device can serve as a potentially safe treatment option for aneurysms of all sizes in the ICA (up to the terminus). Within this current study, the Pipeline™ Vantage Device for the treatment of unruptured or ruptured (>30 days since occurrence), wide-necked intracranial aneurysms located in the ICA (up to the terminus) will be investigated.

Single- Arm Study Design

The proposed study design is a single-arm trial. As with the evaluation of the Pipeline™ Embolization Device in the PUFs IDE study, a randomized controlled trial is not feasible for the evaluation of the Pipeline™ Vantage Device due to the lack of an appropriate control treatment for small/medium and large/giant wide-neck intracranial aneurysms.

The target intracranial aneurysm population is likely to include many aneurysms that can be treated by Pipeline™ Vantage Device but not by any particular single alternative treatment. In the U.S., wide-neck aneurysms are most commonly treated with stent-assisted coiling. Although intracranial stents are available, they are currently approved through a Humanitarian Device Exemption (HDE) and as such have only been proven to demonstrate safety and not effectiveness. Even the recent PMA approved stent, LVIS and LVIS Jr. showed relatively lower effectiveness outcomes with large/giant aneurysms (compared to small/medium aneurysms in the same study) (PMA 170013). As a result, stent-assisted coiling is not a feasible option for the control treatment. The use of coil embolization alone, is predicted to be infeasible in many subjects due to the wide-neck nature of the target aneurysms.

As a result, the study design for the evaluation of the Pipeline™ Vantage Device is a prospective single-arm trial.

Conclusion

In summary, intracranial aneurysms can potentially rupture and lead to serious complications with significantly poor outcomes. SAH resulting from aneurysmal rupture is associated with a high mortality rate of greater than 40%.[1,10] In addition to large and giant aneurysms, which have rupture rates of 18.4% and 50%, small and medium aneurysms warrant consideration for treatment.[99] The average size of ruptured intracranial aneurysms is approximately 6.6-6.8 mm. Small and medium wide-necked intracranial aneurysms are most commonly treated endovascularly with SAC, however, treatment outcomes are sub-optimal. Given the high long-term recanalization and retreatment rates reported with SAC, alternative options with sustained curative effects are necessary. Treatment with the Pipeline™ Embolization Device has 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.[54,55,85,93,127] Data collected in the IntrePED retrospective study and published literature suggests that the Pipeline™ Embolization Device could also be a possible treatment option for small and medium wide-necked intracranial aneurysms.[85,93]

Thus, the aim of the present study is to assess the Pipeline™ Vantage Device beyond the present indication to include wide-neck intracranial aneurysms of all sizes in the ICA (up to the terminus).

7. Product Description

7.1. General

The device under investigation is the Pipeline™ Vantage Embolization Device with Shield Technology™ (Pipeline™ Vantage).

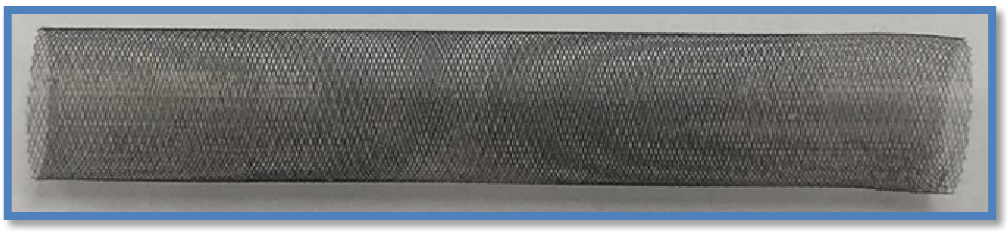
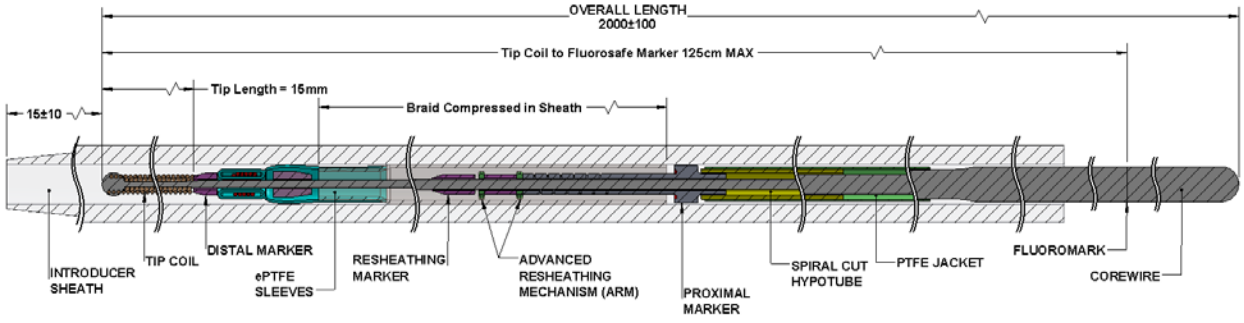
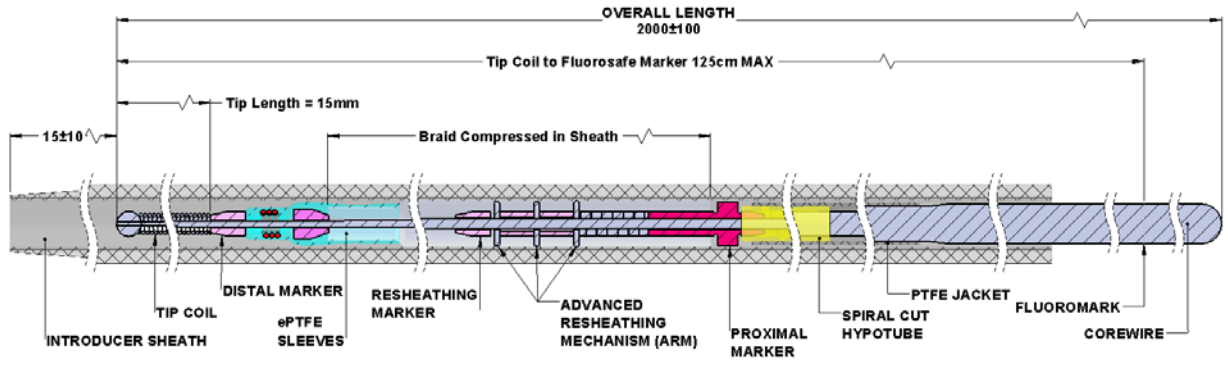


Figure 7-1. Pipeline™ Vantage Embolization Device with Shield Technology™ Implant

The Pipeline™ Vantage consists of a permanent implant (**Figure 7-1**) combined with a guidewire-based delivery system (**Figure 7-2**).



.021" microcatheter compatible system



.027" microcatheter compatible system

Figure 7-2. Pipeline™ Vantage System

The Pipeline™ Vantage implant is a braided, multi-alloy, mesh cylinder woven from Drawn Filled Tubes (DFT). The DFT wires are constructed from a Cobalt-Chromium-Nickel (MP35N LT) that is filled with a platinum core. The woven wires of the device provide approximately 30% metal coverage of the arterial wall surface area. The Pipeline™ Vantage implant is designed for placement in a parent vessel across the neck of an intracranial aneurysm to disrupt pulsatile blood flow from the parent artery into the fundus and to serve as a scaffold upon which endothelial cells can grow. The expanded or unconstrained diameter of the Pipeline™ Vantage implant is 0.25 mm larger than the labeled diameter. The Pipeline™ Vantage Embolization Device includes a surface-modification referred to as Shield Technology™.

The Pipeline™ Vantage implant is assembled on a guide-wire based delivery system and is supplied compressed inside an introducer sheath. The core wire subassembly of the delivery system consists of a stainless-steel core wire, a hypotube and a radiopaque proximal bumper to indicate the proximal end of the implant. The Pipeline™ Vantage implant is mounted at the distal portion of the core wire subassembly. During delivery, the proximal bumper advances the implant, which can be deployed either by forward motion of the delivery wire or by retracting the microcatheter. Advanced Resheathing Mechanism (ARM) is constructed from stainless steel components to allow the user to resheath the implant back into the microcatheter. A Platinum-Iridium restraint is located distal to the resheathing components and is termed the Resheathing Marker to indicate the resheathing limit for the implant. The Distal Protective Subassembly (DPS) is constructed from ePTFE and a Platinum/Tungsten coil to protect the distal portion of the implant while the device is advanced through the microcatheter.

The hypotube is welded at the proximal and distal end to the core wire. The proximal bumper is welded to the core wire and the distal end of the hypotube. The tip coil, distal, and proximal solder joints are manufactured using tin-silver solder material. Refer to **Figure 7-2** for assembled device drawings indicating overall dimensions and marker locations. The Pipeline™ Vantage implant is designed to be delivered through a compatible microcatheter with an inner diameter of 0.021" (0.53 mm) for implant diameters ≤3.50mm and inner diameter of 0.027" (0.69 mm) for implant diameters ≥3.50mm with a minimum length of 135 cm (**Figure 7-2**).

The Pipeline™ Vantage device will be referred to as PED3-XXX-XXX-XX (the first three-digits signify catheter compatibility, the second three-digits refer to the braided implant labeled diameter, and the last two-digits represent the implant length at labeled diameter). The Pipeline™ Vantage will be available in the configurations as listed in **Table 7-1**.

Table 7-1. Pipeline™ Vantage Embolization Device with Shield Technology™ Implant

Legend:	Braided Implant Length (mm)											
Pipeline Vantage .021" Pipeline Vantage .021" & .027" Pipeline Vantage .027"	-10	-12	-14	-16	-18	-20	-25	-30	-35	-40	-45	-50

Braided Implant Diameters (mm)														
	2.50	PED3-021 -250	48	48	48	48	48	48			The values listed indicate the total number of wires in the braided implant.			
	2.75	PED3-021-275	48	48	48	48	48	48						
	3.00	PED3-021-300	48	48	48	48	48	48	48	48				
	3.25	PED3-021-325	48	48	48	48	48	48	48	48				
	3.50	PED3-021-350	48	48	48	48	48	48	48	48	48			
	3.50	PED3-027-350	48	48	48	48	48	48	48	48	48			
	4.00	PED3-027-400	64	64	64	64	64	64	64	64	64	64		
	4.50	PED3-027-450	64	64	64	64	64	64	64	64	64	64		
	5.00	PED3-027-500	64	64	64	64	64	64	64	64	64	64		
	5.50	PED3-027-550	64	64	64	64	64	64	64	64	64	64	64	64
	6.00	PED3-027-600	64	64	64	64	64	64	64	64	64	64	64	64

The Pipeline™ Vantage device is similar to the FDA approved Pipeline™ Flex Embolization Device (P100018/S011). Similar to Pipeline™ Flex, the Pipeline™ Vantage implant is constructed from Cobalt-Chromium-Nickel alloy and platinum material. No new alloys have been introduced in the manufacture of the Pipeline™ Vantage implant. Additionally, the Pipeline™ Vantage device has the same Shield Technology that was utilized in Pipeline™ Flex with Shield Technology™ Device.

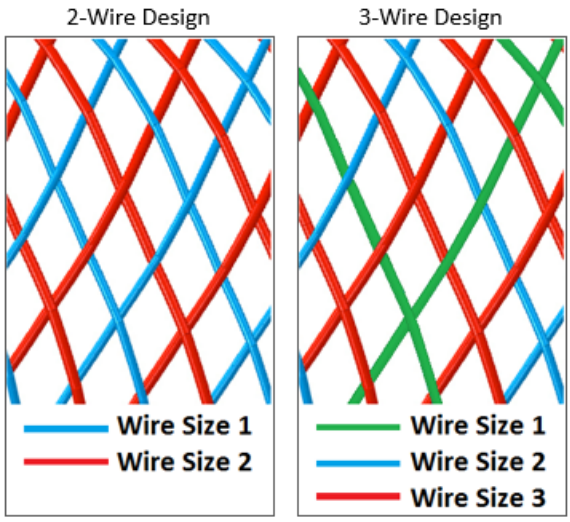
Shield Technology™ (same as Pipeline™ Flex Embolization Device with Shield Technology™)

The Pipeline™ Vantage 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 previously submitted and characterized in the ADVANCE IDE (G170234). The Shield surface modification adds an inert, non-biodegradable phosphorylcholine (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 (the smallest braid wire itself has a thickness of 22860 microns). 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 Phosphorylcholine polymer (Lipidure®-NH01), The implant is also pretreated with (3-Glycidyloxypropyl) trimethoxysilane, which acts a coupling agent to covalently bond the Phosphorylcholine polymer to the implant. Phosphorylcholine is an electrically neutral component of the outer membrane of red blood cells. Because Phosphorylcholine is abundant on the surface of red blood cells, surface modification of a device with Phosphorylcholine physiologically mimics the cell membrane. In vitro assessments of Phosphorylcholine surface modified devices have demonstrated reduced material thrombogenicity.

Wire Design and Braid Pattern

There has been no change to the fundamental braid pattern or wire design of the Pipeline™ Vantage implant when compared to the existing Pipeline™ Flex device. Each implant diameter offered has a unique wire diameter combination of either two or three differently sized wires for optimized deliverability and deployment performance. All Pipeline™ Vantage implants are designed with a 1-over-2 under-2 braid pattern. This is the same pattern utilized by the Pipeline™ Flex braid. Wire diameter distribution and braid pattern is uniform throughout the device regardless of braid orientation or direction. The diagram in **Figure 7-3** shows the wire diameter distribution for both 2- and 3-wire size configurations. The 1-over-2-under-2 pattern can be observed by following the path of a single wire which passes over 2 consecutive wires then passes under the next 2 consecutive wires.

Figure 7-3. Wire Design and Braid Pattern



The key design modifications from the Pipeline™ Flex Embolization Device (Pipeline™ Flex) (P100018/S011) to Pipeline™ Vantage are detailed below.

7.1.1. Key Design Modifications of the Pipeline™ Vantage compared to the Pipeline™ Flex Device

The design enhancements implemented to the Pipeline™ Vantage implant are intended to optimize radiopacity, delivery and resheathing forces, proximal, distal opening, and middle opening. The impact of the design enhancement is most appropriately assessed through non-clinical bench testing such as implant opening, chronic outward force, fatigue, and metal coverage.

7.1.1.1. Larger Implant Diameter/Longer Length

The Pipeline™ Vantage implant is offered in both larger diameters and longer lengths in comparison to the Pipeline™ Flex implant. The Pipeline™ Vantage implant is also offered in a 64-wire configuration (**Table 7-1**).

7.1.1.2. Drawn Filled Tubes/Wire Size

Drawn Filled Tubes of the Pipeline™ Vantage Implant Increases Radiopacity (compared to Pipeline™ Flex)

The currently approved Pipeline™ Flex Embolization Device (Pipeline™ Flex) Implant is a braided, multi-alloy, mesh cylinder woven from a combination of distinct Cobalt-Chromium-Nickel and Platinum/Tungsten monofilaments. The Cobalt-Chromium-Nickel monofilaments provides mechanical benefits to the Pipeline™ Flex implant for shape retention which facilitates braid deployment. The Platinum/Tungsten monofilaments provides visual benefits to the Pipeline™ Flex implant for visualization under fluoroscopy.

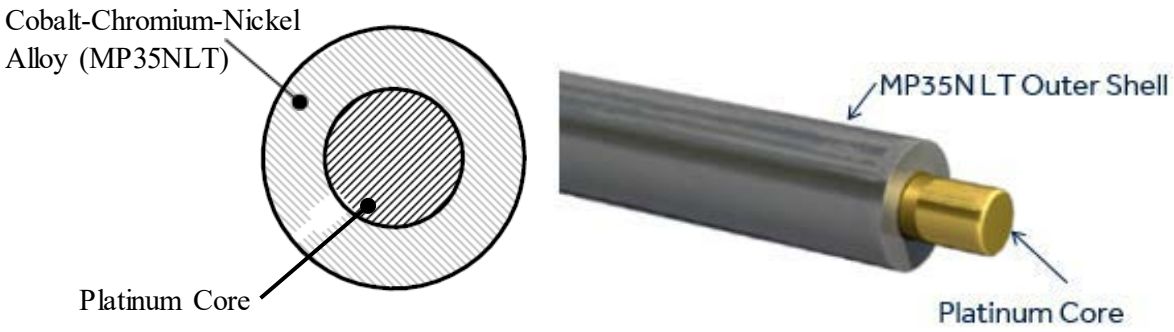


Figure 7-4. Cross sectional view of Drawn Filled Tubes (DFT) (Left), Drawn Filled Tubes (DFT) Visualization (Right) of the Pipeline™ Vantage Device

In comparison, the Pipeline™ Vantage implant is a braided, multi-alloy, mesh cylinder woven from Drawn Filled Tubes (DFT). The DFT are cylindrical wires constructed from Cobalt-Chromium-Nickel alloy tube filled with a Platinum core. The outer element of the DFT is the same alloy as the Cobalt-Chromium-Nickel alloy used in the monofilaments in the Pipeline™ Flex implant. The inner element (or core) of the drawn filled tube is 99.95% Platinum (**Figure 7-4**). The Pipeline™ Flex Embolization Device Implant Platinum/Tungsten monofilaments are 92% Platinum and 8% Tungsten.

Removal of the Platinum/Tungsten monofilaments optimizes the opening of the implant by incorporating the mechanical benefits of the cobalt-chromium-nickel alloy into all wires that comprise the braided mesh of the Pipeline™ Vantage device. The DFT wires also optimize the visual benefits of platinum by incorporating a 99.95% Platinum fill within all wires that comprise the braided mesh of the Pipeline™ Vantage. **Figure 7-4** depicts the Platinum core extending beyond the outer shell to distinguish the two metallic components; however, each of the alloys have the same termination point in the finished device.

Decreased Wire Diameter of the Pipeline™ Vantage Implant Optimizes Deliverability (compared to Pipeline™ Flex)

The Pipeline™ Vantage will be offered in diameter range of 2.50 to 6.00 mm in comparison to Pipeline™ Flex's 2.50 to 5.00 mm. For each implant diameter offered, the average wire diameter has been reduced (**Table 7-2**). This reduction in wire diameter minimizes the crimped braid profile, reduces the effective wall thickness of the implant and optimizes the metal coverage. The reduction in wire diameter was engineered with the intent to enhance deliverability and promote the healing response once delivered. With the incorporation of Cobalt-Chromium-Nickel alloy into all wires of the braid by means of DFT, reduction in wire diameter was achieved with improved opening performance of the implant itself. The woven wires of the Pipeline™ Vantage implant provide approximately 30% metal coverage of the arterial wall. The reduction in wire diameter, increase in wire count (4.0-6.0mm braids), and optimized braid angle resulted in a marginal reduction in metal coverage, without sacrificing pore density.

Table 7-2. Implant Wire Comparison of Pipeline™ Flex and Pipeline™ Vantage

Labeled Implant Diameter (mm)	Implant Wire Diameter (inches)				Implant Braid Angle (degrees)	
	FLEX		VANTAGE		FLEX	VANTAGE
2.50	Wire 1	24 x 0.0010"	Wire 1	24 x 0.0009"	61°	61°
	Wire 2	24 x 0.0011"	Wire 2	24 x 0.0011"		
2.75	Wire 1	24 x 0.0010"	Wire 1	24 x 0.0009"	58°	58°
	Wire 2	24 x 0.0011"	Wire 2	24 x 0.0011"		
3.00	Wire 1	24 x 0.0010"	Wire 1	24 x 0.0009"	56°	57°
	Wire 2	24 x 0.0012"	Wire 2	24 x 0.0012"		
3.25	Wire 1	24 x 0.0011"	Wire 1	24 x 0.0010"	53°	54°
	Wire 2	24 x 0.0012"	Wire 2	24 x 0.0012"		
3.50	Wire 1	24 x 0.0011"	Wire 1	24 x 0.0010"	52°	53°
	Wire 2	24 x 0.0013"	Wire 2	24 x 0.0013"		
4.00	Wire 1	12 x 0.0011"	Wire 1	16 x 0.0009"	48°	55°
	Wire 2	36 x 0.0013"	Wire 2	16 x 0.0010"		
	N/A		Wire 3	32 x 0.0011"		
4.50	Wire 1	24 x 0.0012"	Wire 1	32 x 0.0010"	45°	52°
	Wire 2	24 x 0.0014"	Wire 2	32 x 0.0012"		
5.00	Wire 1	12 x 0.0012"	Wire 1	32 x 0.0010"	43°	50°
	Wire 2	12 x 0.0013"	Wire 2	32 x 0.0013"		
	Wire 3	24 x 0.0014"	N/A			
5.50	N/A		Wire 1	16 x 0.0010"	N/A	49°
			Wire 2	16 x 0.0012"		
			Wire 3	32 x 0.0014"		
6.00	N/A		Wire 1	32 x 0.0010"	N/A	48°
			Wire 2	32 x 0.0015"		

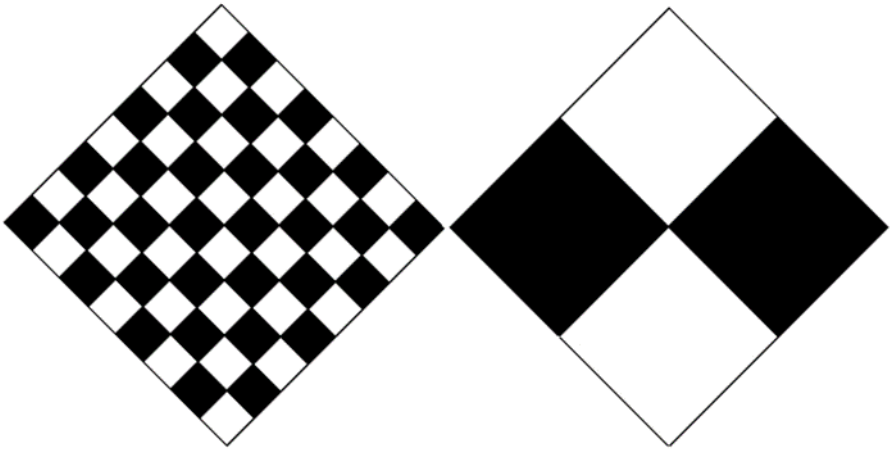
7.1.1.3. Wire Count (available in 48-wire and 64-wire configuration)

The Pipeline™ Vantage implant will be offered in diameter range of 2.50 to 6.00 mm. To accommodate for the diameter range, the braided implant is offered in a 48-wire and a 64-wire configuration (**Table 7-1**). The 48-wire configuration is offered for braid diameters ≤3.5 mm and the 64-wire configuration is offered for braid diameters ≥4.0 mm. Whereas, the currently approved Pipeline™ Flex is available in the diameter range 2.50 to 5.00 mm and is only offered in a 48-wire configuration. The 64-wire configuration enhances the ability of the implant to open upon deployment from the delivery system.

In addition to the 64-wire configuration, individual pore sizes were decreased while pore density was increased for the larger diameter implants (**Figure 7-5** and **Table 7-3**). Pore density, which is defined as the number of pores per mm^2 (pores/mm^2) is considered to determine efficacy for flow diverters.[128,129]

In **Figure 7-5**, the white diamonds represent pores and the black diamonds represent metal. The porosity of the two are identical at 50%. However, the image on the left has a higher pore density (sixteen-fold) than the image on the right. The concept of pore density (or pore size) is important for the biological response of the artery to the implant since pore density determines the properties of the scaffold over which cellular elements proliferate and populate.[128]

Figure 7-5. Pore Density of the Pipeline™ Vantage Device (left) and the Pipeline™ Flex Device (right)



In the figure above, the white diamonds represent pores and the black diamonds represent metal. The porosity of the two are identical at 50%. However, the image on the left has a higher pore density (sixteen-fold) than the image on the right.

Table 7-3. Implant Property Comparison of Pipeline™ Flex and Pipeline™ Vantage

Labeled Implant Diameter	Pore Density (pores/mm^2)		Metal Coverage (%)		Average Wall Thickness (µm)		Foreshortening (%)	
	FLEX	VANTAGE	FLEX	VANTAGE	FLEX	VANTAGE	FLEX	VANTAGE
2.50	33	33	30	29	53	51	48	47
2.75	29	29	29	27	53	51	50	49

Labeled Implant Diameter	Pore Density (pores/mm^2)		Metal Coverage (%)		Average Wall Thickness (µm)		Foreshortening (%)	
	FLEX	VANTAGE	FLEX	VANTAGE	FLEX	VANTAGE	FLEX	VANTAGE
3.00	26	25	28	27	56	53	52	50
3.25	22	22	29	27	58	56	54	53
3.50	20	20	29	27	61	58	56	55
4.00	17	26	28	27	64	52	59	53
4.50	14	22	27	27	66	56	61	52
5.00	12	18	26	26	67	58	63	51
5.50	N/A	15	N/A	27	N/A	64	N/A	54
6.00	N/A	13	N/A	25	N/A	64	N/A	58

7.1.1.4. Pipeline™ Vantage Delivery System

Similar to the Pipeline™ Flex, the Pipeline™ Vantage implant is mounted on a guide-wire based delivery system approximately 200 cm long and is supplied compressed inside an introducer sheath. The primary component remains a 304-stainless steel core wire that extends from the proximal end of the delivery system to the distal tip. Like that of Pipeline™ Flex, a spiral cut 304L stainless steel hypotube is mounted over the core wire and covered with a polytetrafluoroethylene (PTFE) jacket. The below design enhancements implemented to the Pipeline™ Vantage Delivery System are intended to enhance tactile feedback, deliverability, and include a low-profile delivery system to enable compatibility with micro catheters that have an inner diameter of 0.021" for delivering implants with a diameter of ≤3.50 mm.

7.1.1.4.1. Corewire-based Delivery System

The Pipeline™ Vantage Delivery System utilizes a single tapered core wire subassembly design, including a larger proximal portion for .027" microcatheter compatible sizes for enhanced pushability when compared to Pipeline™ Flex Embolization Device. In comparison, the existing Pipeline™ Flex delivery system uses separate proximal and distal core wires secured by the spiral cut hypotube.

7.1.1.4.2. Advanced Resheathing Mechanism

The Pipeline™ Vantage delivery system incorporates a newly designed Advanced Resheathing Mechanism (ARM) that allows the user to resheath the implant up to two times. The ARM is a stainless-steel subassembly that engages the pores of the braid with gear-like functionality to enable resheathing with enhanced reliability. During resheathing, the user holds the delivery wire and simultaneously advances the microcatheter to recapture the implant. The ARM secures the implant within the microcatheter to facilitate resheathing. In comparison, the existing Pipeline™ Flex Delivery System uses a friction based resheathing pad which exerts a constant radial force against the implant during both delivery and resheathing.

7.1.1.4.3. Distal Protective Subassembly (DPS)

The Pipeline™ Vantage delivery system also includes a Distal Protective Subassembly (DPS), like that of Pipeline Flex, which protects the distal portion of the implant while the device is advanced through a

microcatheter. The DPS is comprised of protective sleeves made from ePTFE and a Platinum-Tungsten coil. The sleeves are attached to the radiopaque coil to allow the DPS to be mounted over the distal portion of the core wire and cover the distal end of the Pipeline™ Vantage braid. The coil has been designed to be smaller in outer diameter compared to Pipeline™ Flex to enable compatibility with 0.021" microcatheters.

7.1.1.4.4. Corewire Subassembly

The Pipeline™ Vantage Corewire Subassembly includes the core wire, spiral cut hypotube, and proximal bumper. PTFE shrink tubing covers the spiral cut hypotube and tapered section of the core wire to provide a smooth lubricious liner to facilitate navigation. The PTFE shrink tube length is longer for devices compatible with .021" microcatheter. The hypotube length and the overall length of the delivery system remains constant for all sizes. The implant is mounted on the distal portion of the core wire and is compressed inside an introducer sheath prior to delivery. The radiopaque proximal bumper is secured at the distal end of the hypotube to indicate the proximal end of the implant. During delivery, the proximal bumper advances the implant, which can be deployed either by forward motion of the delivery wire or by retracting the microcatheter.

7.2. Manufacturer

The manufacturer of the Pipeline™ Vantage Device is Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic) located at 9775 Toledo Way, Irvine, CA 92618, United States.

7.3. Pre-clinical Summary

7.3.1. Biocompatibility Summary

Biocompatibility was conducted for the Pipeline™ Vantage Implant and Delivery System. The Pipeline™ Vantage Implant and Delivery System met the acceptance criteria specified per ISO 10993-1:2009 and FDA Guidance on the *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management* issued on June 16, 2016.

7.3.2. Animal Studies Summary

7.3.2.1. 7-Day Porcine Study Summary:

Test report: D00026019

Objective: Assess the acute inflammatory tissue response, thromboembolism, and endothelization of Pipeline™ Vantage as compared to Pipeline™ Flex and verify the conformance of the Pipeline Vantage Delivery system to established biocompatibility requirements.

Number of animals & devices: Seven (7) animals were used in this study. One animal was excluded due to failure to meeting exclusion criteria per protocol. Six (6) animals were successfully implanted with two paired test and control braids (four devices per animal) in like vessels.

Endpoint: 7-day survival

Procedure: The Pipeline™ Vantage Delivery System was tested in six porcine models by navigating the Pipeline™ Vantage Delivery System to the target location, unsheathing and resheathing the Pipeline™ Vantage Implant (a maximum of three times) followed by a 30-minute dwell time. Following the 30-minute dwell, the Pipeline™ Vantage Delivery System was removed and the 7-day survival time point began.

Results:

1. All animals survived to their designated 7-day survival time point. Study met the protocol specified acceptance criteria.
2. No safety risks were identified with Pipeline™ Vantage when compared to Pipeline™ Flex and it was determined that there is a non-inferior difference of < 20% for Pipeline™ Vantage as compared to Pipeline™ Flex.

Conclusion: The pathology findings of the study are supportive of an acceptable safety profile for all braids and delivery systems, with no safety concerns identified in the animal model.

7.3.2.2. 90-Day Porcine Study Summary

Test report: D00026003

Objective: Demonstrate the safety, efficacy, and usability of the of Pipeline™ Vantage as compared to Pipeline™ Flex at 90 days.

Number of animals & devices: Six (6) animals were successfully implanted with two paired test and control braids (four devices per animal) in like vessels.

Endpoint: 90-day survival

Procedure: Six (6) animals were successfully implanted with two paired test and control braids (four devices per animal) in like vessels.

Results:

1. All animals survived to their designated time point. The study met the protocol specified acceptance criteria.
2. No safety risks were identified with Pipeline™ Vantage when compared to Pipeline™ Flex and it was determined that there is a non-inferior difference of < 20% for the Pipeline™ Vantage as compared to Pipeline™ Flex.
3. No significant acute and/or sub-acute complications from implantation to the 90-day survival time point were noted.

Conclusion: Findings of the study support an acceptable safety profile for all braids and delivery systems, with no safety concerns identified in the animal model.

7.3.2.3. 90-Day Laprine (Rabbit) Study Summary:

Test report: D00026006

Objective: Demonstrate the safety, efficacy, and usability of Pipeline™ Vantage as compared to Pipeline™ Flex at 90 days.

Number of animals & devices: Thirty-six (36) animals had aneurysms created using elastase in the right carotid artery (one aneurysm per model) ~41-48 days prior to implantation.

Endpoint: 90-day survival

Procedure: Prior to the study, three animals died, leaving a total of thirty-three available. Throughout the study, three animals were omitted due to exclusion criteria (e.g. incorrect aneurysm formation). A single device was successfully implanted in the right brachiocephalic/right subclavian artery across the neck of the aneurysm in thirty animals as well as three devices successfully implanted across the ostia of lumbar arteries in the descending aorta.

Results:

1. The remaining twenty-nine animals survived to their designated survival time point.
2. No safety risks were identified with Pipeline™ Vantage when compared to Pipeline™ Flex and it was determined that there is a non-inferior difference of < 20% for the Pipeline™ Vantage as compared to Pipeline™ Flex.
3. No significant acute and/or sub-acute complications from implantation to the 90-day survival time point were noted.

Conclusion: Findings of the study support an acceptable safety profile for all braids and delivery systems, with no safety concerns identified in the animal model.

7.3.2.4. 180-Day Laprine (Rabbit)Study Summary:

Test report: D00026887

Objective: Demonstrate the safety, efficacy, and usability of Pipeline™ Vantage as compared to Pipeline™ Flex at 180 days.

Number of animals & devices: Thirty-six (36) animals had aneurysms created using elastase in the right carotid artery (one aneurysm per model) ~21-48 days prior to implantation. Two (2) of thirty-six (36) animals were intended as backup animals. Three (3) of thirty-four animals (were excluded following baseline imaging due to meeting protocol exclusion criteria.

Endpoint: 180-day survival

Procedure: Thirty-one (31) animals were implanted with the test or control devices were implanted in the right brachiocephalic/right subclavian artery (BCA/RSC) across the neck of an aneurysm of each animal. Of the 31 animals with test or control devices implanted, four (4) were excluded from the study.

Results:

1. Three animals died within 1-2 days post implant procedure and were most likely procedure related (unrelated to treatment or device).

2. One (1) animal was humanely euthanized on day 27 due to declining health (fractured left femur) and the cause of this finding was considered unrelated to the device.
3. A total of twenty-seven (27) animals completed this study at the intended 180 time point.
4. No safety risks were identified with Pipeline™ Vantage when compared to Pipeline™ Flex and it was determined that there is a non-inferior difference of < 20% for the Pipeline™ Vantage as compared to Pipeline™ Flex.
5. No significant acute and/or sub-acute complications from implantation to the 180-day survival time point were noted.

Conclusion: Findings of the study support an acceptable safety profile for all braids and delivery systems, with no safety concerns identified in the animal model.

7.4. Packaging

Pipeline™ Vantage is an investigational device. Pipeline™ Vantage is limited by Federal (or United States) law to investigational use and is labeled as such.

Physicians using the device should follow the current IFU version at the site.

7.5. Intended Population

The Pipeline™ Vantage Embolization Device with Shield Technology™ is intended for endovascular treatment of adults (22 years of age or older) with wide-necked intracranial aneurysms located in the internal carotid artery (up to the terminus).

7.6. Contraindications

- Patients with active bacterial infection
- Patients in whom dual antiplatelet and/or anticoagulation therapy (aspirin and clopidogrel) is contraindicated.
- Patients who have not received dual antiplatelet agents prior to the procedure.
- Patients in whom the parent vessel size does not fall within the indicated range.

7.7. Product Training Requirements

Pipeline™ Vantage should only be used by attending physicians trained in percutaneous, intravascular techniques and procedures at medical facilities with the appropriate fluoroscopic equipment. Fellows are not permitted to implant Pipeline™ Vantage or any other adjunctive device for the treatment of aneurysms during the study procedure. Physicians who participate in this study are responsible for implanting the study device and are required to self-attest to completing a minimum of 20 cases with Pipeline™ Flex Embolization Device. Prior to implantation of the Pipeline™ Vantage, implanting Investigator(s) will be trained on the CIP and IFU.

7.8. Product Accountability

Pipeline™ Vantage is tracked by lot number and usage of all study devices will be recorded. All devices must be kept in a secured location with limited access complete accountability for each device must be maintained, including shipping, receiving and return of the devices. Any unused devices must be returned to Medtronic at the conclusion of the study or upon product expiration.

8. Selection of Subjects

8.1. Study Population

The study population will consist of subjects with unruptured or ruptured (>30 days since occurrence) wide-neck intracranial aneurysms in the ICA.

For subjects with more than one aneurysm requiring treatment, the following guidance is to be followed for subjects to be enrolled in the study.

- If more than one aneurysm can be covered by a single Pipeline™ Vantage Device, the largest aneurysm meeting study criteria will be designated the target aneurysm. For equal sized aneurysms, the Core Lab will designate the target aneurysm. Overlapping of Pipeline™ Vantage device (i.e., stacking of devices) to be allowed if the investigator determines that it is required to cover the target aneurysm neck adequately. A maximum of 3 Pipeline™ Vantage Devices may be stacked at any point in the arterial vessel.

- Provided the subject has more than one aneurysm and all aneurysms requiring treatment cannot be covered by a single Pipeline™ Vantage Device (unless overlapping with devices is for covering the target aneurysm neck adequately), AND the non-target aneurysms are outside of the affected territory, the non-target aneurysms should be treated first. After waiting at least 30 days per exclusion, the subject may return for treatment of the target aneurysm in the study with the Pipeline™ Vantage Device.

- If the subject has more than one aneurysm and all aneurysms requiring treatment cannot be covered by a single Pipeline™ Vantage Device (unless overlapping with devices is for covering the target aneurysm neck adequately), AND the non-target aneurysms is inside the affected territory of the target aneurysm, the subject is ineligible for this study per exclusion criterion.

8.2. Subject Enrollment

Subjects are considered enrolled in the study when the subject (or subject's legally authorized representative) signs the Informed Consent Form. Each site will follow the same protocol, and no single site will be allowed to enroll more than 20% of the total subjects.

8.3. Inclusion Criteria

Subjects must meet all of the following Imaging (determined by the core lab) and Clinical inclusion criteria:

Imaging Criteria (Core Lab Assessed)

1. Subject has a target intracranial aneurysm located in the internal carotid artery (up to the terminus).
2. Subject has a target intracranial aneurysm with an aneurysm neck ≥4mm or a dome-to-neck ratio of < 2.
3. Subject has a target intracranial aneurysm that has a parent vessel with diameter 1.5–5.0 mm distal/proximal to the target intracranial aneurysm.

Clinical Criteria

4. Subject (or subject's legally authorized representative) has provided written informed consent using the IRB/REB and Medtronic approved Informed Consent Form and agrees to comply with protocol requirements. HIPAA/data protection authorization has been provided and signed by the subject (or subject's legally authorized representative).
5. Age 22-80 years at the time of consent.
6. Life expectancy ≥3 years
7. Subject has a mRS ≤ 2 at baseline to be determined by a certified independent assessor at the site
8. Subject has already been selected for endovascular treatment of the target aneurysm.
9. Subject's last recorded $P2Y_{12}$ reaction units (PRU) value is between ≥60 and ≤200 prior to study procedure. For OUS sites, a TEG test may be carried out instead of the PRU test (depending on PRU test availability). In cases where TEG test is carried out, the subject should have a pre-procedure therapeutic ADP% between >30% to <90%.
10. Subject has multiple increased risk factors for intracranial aneurysm rupture, including but not limited to, aneurysm morphology, smoking, hypertension, diabetes, age, prior and/or family history of rupture, and/or history of subarachnoid hemorrhage that may result in a benefit risk profile of endovascular treatment to outweigh the risks of intracranial aneurysm rupture during the subject's expected lifetime if left untreated.

8.4. Exclusion Criteria

The subject must not meet any of the following exclusion criteria:

Imaging Criteria (Core Lab Assessed)

11. Subject has internal carotid artery bifurcation aneurysm.
12. Aneurysms that arise from the Posterior Communicating Artery (PComm).
13. The internal carotid artery aneurysms of the C7 segment will be excluded under the following conditions:
    a. Observed fetal posterior communicating artery (PComm) (A PComm of fetal origin is defined as a small, hypoplastic, or absent P1 segment of the posterior cerebral artery (PCA) with the PComm artery supplying a majority of blood flow to the P2 and higher order segments of the PCA)
    b. PComm overlapping with the aneurysm neck
    c. PComm branch arising from the dome of the aneurysm
14. Subject has aneurysm arising from internal carotid artery but is primarily fed by posterior circulation (i.e., retrograde flow from the basilar artery) as confirmed by DSA

Clinical Criteria

15. Subject requires treatment of another aneurysm (with another treatment modality) within the affected territory of the target aneurysm during the study period.
16. Subject has received an intracranial implant (e.g. coils) in the area of the target intracranial aneurysm within the past 6 months prior to the study procedure.
17. Subject has had a SAH and/or target aneurysm rupture in the past 30 days prior to the study procedure.
18. Subject has undergone a surgery including endovascular procedures in the last 30 days prior to the study procedure.
19. Vessel characteristics (e.g. severe tortuosity, stenosis, morphology) that preclude safe endovascular access to the aneurysm to allow for necessary access to treat with the study device.

20. 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, re-treatment, or device movement.

21. Subject has active vasospasm, malignant brain tumor or vascular malformation (e.g. arteriovascular malformation).

22. History of major bleeding disorder (based on coagulation profile and platelet count) and/or subject presents with signs of active bleeding.

23. Subject requires adjunctive device use (e.g. coils) during the index procedure.

24. Subject has extradural target aneurysm <12mm which is not symptomatic or not exhibiting aneurysm growth (exception: unless it is a fusiform aneurysm <12 mm i.e., asymptomatic extradural fusiform aneurysms <12 mm can be included).

25. Any known contraindication to treatment with the Pipeline™ Vantage Embolization Device with Shield Technology™, or use of antiplatelet therapy including:

    d. Active bacterial infection

    e. Contraindication to DAPT agents

26. Pre-existing stent is in place in the parent artery at the target intracranial aneurysm location.

27. Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction.

28. The Investigator determines that the health of the subject or the validity of the study outcomes (e.g., high risk of neurologic events, conditions that may increase the chance of stroke) may be compromised by the subject's enrollment.

29. Subject is pregnant or wishes to become pregnant during the first year of study participation.

30. 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.

31. Subject with known allergy to platinum or cobalt chromium alloy (including the major elements platinum, cobalt, chromium, nickel or molybdenum).

32. History of previous acute ischemic stroke

33. Subject is unable to undergo DSA or CTA imaging at follow-up.

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 timing is provided in **Table 9-1**. Scheduled visits occurring outside of the specified date range will be considered clinical protocol deviations. After the clinical investigation has been completed, subjects will be followed according to standard of care.

Table 9-1. Visit and Assessment Schedule

Visits		Baseline	Procedure		Discharge exam	Follow-up					
			Pre- (Day 0)	Post- (Day 0)	Day 1-7	30-day	180-day	1-year	2-year	3-year	Un-scheduled
Assessments	Time Window	-7 to -30 days	Day 0	Day 0	1-7 days	±7 days	±30 days	± 56 days	± 56 days	± 56 days	
Assess Inclusion/Exclusion		X	X								
Informed Consent		X									
Demographics		X									
Medical History		X									
Risk Factors		X[1]									
Pregnancy Test			X[6]					X[6]	X[6]	X[6]	
WBC		X[10]									
Platelet count		X[10]									
Coagulation Profile (PT/aPTT)		X[10]									
Platelet Reactivity Testing			X[7]								
Protocol Specified Medications		X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X
DSA Imaging		X[2]	X[9]	X			X[4]	X	X[3]	X[3,4]	X[4]
MRA									X[3]	X[11]	X[4]
CTA							X[11]			X[11]	X[4]
Modified Rankin Scale (mRS)			X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5,8]
NIH Stroke Scale			X					X			X[8]
Neurological Exam		X			X	X	X	X	X	X	X
Assess Adverse Events		X[12]	X	X	X	X	X	X	X	X	X

[1] Risk factors to be assessed and collected for all subjects regardless of aneurysm size

[2] The baseline DSA, CTA OR MRA images must be taken no more than 90 calendar days prior to the procedure and core lab can use this for diagnostic or eligibility determination. Note that the pre-procedure exam for imaging would be with a DSA.

[3] If aneurysm is not occluded at 1 year or subsequent follow-up visits, DSA must be performed at 2- and 3- year follow-up. If child bearing potential woman becomes pregnant during the study, subject may obtain MRA without contrast instead of DSA.

[4] To be collected if conducted per standard of care

[5] mRS to be carried out by a certified independent assessor at the site. To become a certified independent assessor for mRS, the assessor should have passed a certification exam via online portal BlueCloud (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 trial and will have no other responsibilities or duties associated with the trial.

[6] Pregnancy test (serum or urine) only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test. At the 2- and 3- year follow-up, pregnancy test is only required for female subjects of childbearing potential that are undergoing DSA imaging.

[7] If PRU is found below 60 or above 200 on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is scheduled >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the PRU must be repeated, however, the baseline measurements may be repeated per standard of care at the treating hospital. For OUS sites, a TEG test may be carried out instead of the PRU test (depending on PRU test availability). In cases where TEG test is carried out, the subject should have a pre-procedure therapeutic ADP% between >30% to <90%. If ADP% is <30% or >90% on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is schedule >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the TEG measurements must be repeated but the other baseline measurements may be repeated per standard of care at the treating hospital. Note: treating physicians should also assess if ARU testing is required to assess aspirin responsiveness based on subject condition and response (per standard of care)

[8] For stroke events, mRS should be performed minimum of 90 days post event and NIHSS should be performed at the time of event and 24 hours after event.

[9] DSA at pre-procedure to be used for final aneurysm measurements can be done any time prior to the index procedure

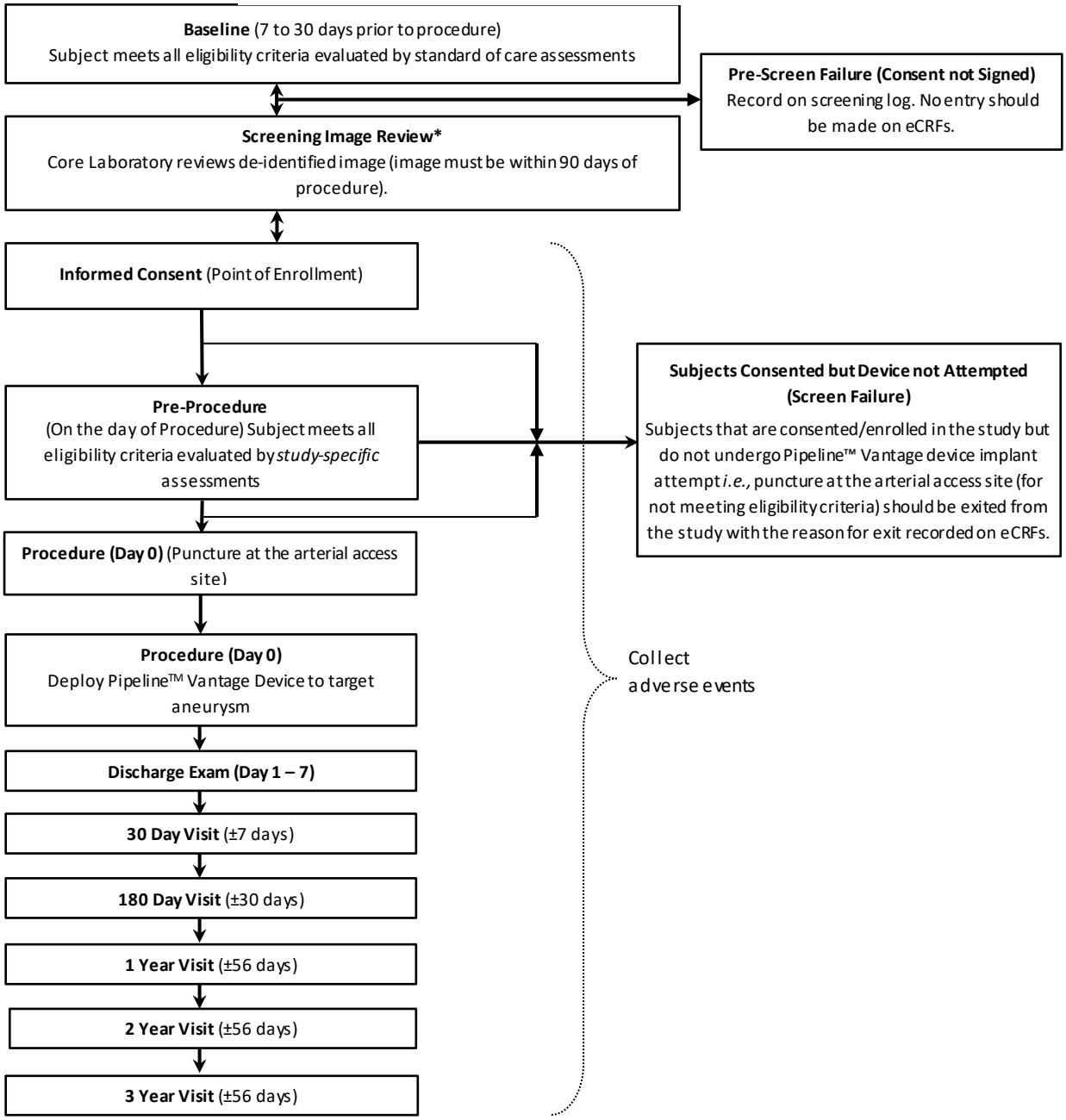
[10] Can be done any time prior to the index procedure

[11] If DSA not collected per standard of care, subject must undergo CTA imaging. For follow-up images after the 1-year follow-up, under certain conditions, MRA imaging may be obtained instead of a DSA or CTA imaging e.g., subjects with iodine allergies, borderline renal function, pregnancy, or concerns over excessive radiation. The justification for using MRA over DSA or CTA should be captured in the case report form. Precaution: DSA or CTA imaging are preferred over MRA imaging due to the risk of reduced image quality (artifact) when attempting to visualize near or inside the implanted device with MRA imaging. Note that MRA should not be used for any follow-up imaging within 1-year

[12] Assess adverse events after informed consent is signed.

An overview of the study procedures is shown in **Figure 9-1**

Figure 9-1. Overview of Study Procedures



*As permitted by the IRB/REB, de-identified images taken per standard of care may be sent to the core lab for screening committee review prior to informed consent.

9.2. Baseline

The baseline visit must occur 7 to 30 days prior to the procedure day.

During baseline, the following assessments should be completed.

- Inclusion/exclusion criteria assessment
- Informed consent
- Demographics: age, gender, ethnicity and race
- Medical and surgical history
- Risk factors, including aneurysm history; note that risk factors to be collected for all enrolled subjects regardless of the aneurysm size
- Platelet count and WBC (can be done any time prior to index procedure)
- Coagulation Profile (can be done any time prior to index procedure)
- Protocol specified Medications
- Record concomitant medications
- DSA, CTA or MRA imaging (The baseline DSA, CTA or MRA images must be taken no more than 90 calendar days prior to the procedure)
- Neurological Exam
- Assessment of Adverse Events (Assess adverse events after informed consent is signed)

This data will be collected in the electronic case report forms (eCRF) for all subjects enrolled and treated in the study. The de-identified images will be sent to the Core Lab for review. Enrolled subjects determined to be ineligible for the study prior to the puncture at the arterial access site on the day of the study procedure (Day 0), will only require the reason for the eligibility failure and study exit to be recorded in the eCRF. No further eCRFs are required.

9.2.1. Baseline Imaging

Baseline imaging (DSA, CTA, or MRA) must be taken within the 90 calendar days prior to the planned procedure date and core lab can use this for eligibility determination. As permitted by the IRB/REB, de-identified images taken per standard of care may be sent to the core lab for screening committee review prior to informed consent.

At Screening, all of the following images shall be collected:

- Imaging showing the aneurysm measurements

Screening imaging to characterize the aneurysm **must be reviewed and approved by the Core Lab**. As permitted by the IRB/REB, de-identified images taken per standard of care may be submitted to the Core Lab prior to the subject (or subject's legally authorized representative) signing the Informed Consent Form.

9.2.2. Medical History

Medical/surgical history and aneurysm specific history will be collected 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. Risk factors will be assessed and collected for all subjects regardless of aneurysm size.

Aneurysm history and detailed symptoms and signs present at baseline shall be collected as medical history. Any worsening of these symptoms after the point of consent shall be collected as adverse events.

9.2.3. Concomitant Medications

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

1) All medications the subject is on at the time of enrollment (consent)
2) Medications received on the study procedure day (Day 0)–further detail regarding these medications is provided in Section 9.2.4 and 9.6
3) Any new medications taken for intervention of study reportable events of interest
4) Change in previously recorded concomitant medications after the study procedure (Day 0) through study exit

9.2.4. Pre-Procedure Antiplatelet/Anticoagulation agents

All protocol specified medications will be collected from the point of consent or from the first day of anticoagulation/antiplatelet treatment (whichever is earlier) through study exit.

The following dose of antiplatelet agents will be given before treatment with the Pipeline™ Vantage Device as defined below. The DAPT regimen should be taken for a minimum of 5 consecutive days prior to the index procedure

- **Aspirin:** 81-325 mg daily
- **$P2Y_{12}$ Platelet Inhibitor:** Only the following agents shall be utilized:

- **Clopidogrel:** 75–100 mg daily

In situations where subjects are hypo-responders to Clopidogrel:

- **Prasugrel** (Only for subjects <75 years of age and should not be used in subjects with a history of TIA or stroke): 5-10 mg once daily

Or

- **Ticagrelor:** 60-90 mg twice daily with a maximum daily dose of Aspirin not exceeding 100 mg

The PRU value will be collected on eCRFs and treatment with the Pipeline™ Vantage Device can only be undertaken when PRU levels within therapeutic of ≥ 60 and ≤200 is achieved. If PRU is found below 60 or above 200 on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline PRU measurements must be repeated if the next procedure is scheduled >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the PRU measurements must be repeated but the other baseline measurements may be repeated per standard of care at the treating hospital. For OUS sites, a TEG test may be carried out instead of the PRU test (depending on PRU test availability). In cases where TEG test is carried out, the subject should have a pre-procedure therapeutic ADP% between >30% to <90%. If ADP% is <30% or >90% on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is schedule >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the TEG measurements must be repeated but the other baseline measurements may be repeated per standard of care at the treating hospital.

Note: Treating physicians should also assess if ARU testing is required to assess aspirin responsiveness based on subject condition and response (per standard of care).

9.3. Subject 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.

Pre-screening (visit to collect standard of care assessments according to institution) may be permitted prior to informed consent.

The Investigator(s) and/or staff delegated for this task are responsible for obtaining written informed consent and the HIPAA/data protection authorization from each potential subject before any study-

specific procedures required by the clinical protocol are performed. Informed consent should be obtained in written format and using a form approved by the local IRB/REB and Medtronic. All subjects (or their legally authorized representative) must sign and date the Informed Consent Form and the HIPAA/data protection authorization prior to any procedures/tests that go beyond pre-screening assessments associated with the standard of care for subjects with intracranial aneurysms and before any study-related treatment assessments are administered and subject-related health information is entered into the study database. The Informed Consent Form and HIPAA/data protection authorization should be given to the subject (or their legally authorized representative) in a language he/she is able to read and understand.

Prior to inclusion in the study, it is the responsibility of the Investigator and/or staff delegated to this task to give each subject (or subject's legally authorized representative) full and adequate verbal and written information regarding the objective of this study and the confidentiality of the data collected. The process of obtaining informed consent must also be documented in the subject's file. The original or a copy of the signed Informed Consent Form should be filed in the hospital/clinical chart or with the subject's study documents. A copy of the consent and HIPAA/data protection authorization must be provided to the subject.

A thorough explanation will be provided to the subject (or subject's legally authorized representative) as to the nature and objectives of this study. Details of the study will be included according to country regulatory requirements which include but are not limited to the following:

- Purpose of the study
- Alternative treatments
- Procedures of the study including the need to return for 30-day, 180-day, 1-year, 2-year, and 3-year follow-up visits
- Participation is voluntary, and there is no penalty for withdrawal
- Potential risks and benefits of participation
- Compensation and expenses to subject
- Contact information to ask questions or voice concerns

Medtronic will maintain the sample Informed Consent Form and all materials used to consent including the HIPAA/data protection authorization within the Trial Master File.

9.4. Pre-Procedure Assessment

Subjects must undergo the device placement procedure within 30 calendar days of completion of all baseline assessment tests and procedures. On the day of the procedure and prior to treatment, the subject will again be evaluated and the following data shall be collected and recorded in the eCRF:

- Inclusion/exclusion criteria assessment
- Pregnancy test (Pregnancy test (serum or urine) only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test)
- Platelet count (can be done any time prior to the procedure)
- Platelet reactivity testing (If PRU is found below 60 or above 200 on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is schedule >30 days from the initial planned procedure. If procedure is performed <30 days from the initial planned procedure, the PRU measurements must be repeated but the other baseline measurements may be repeated per standard of care at the treating hospital). For OUS sites, a TEG test may be carried out instead of the PRU test (depending on PRU test availability). In cases where TEG test is carried out, the subject should have a pre-procedure therapeutic ADP% between >30% to <90%. If ADP% is <30% or >90% on the day of the procedure, the procedure should be delayed until it is within therapeutic range. In such cases, baseline measurements should be repeated if the next procedure is schedule >30 days from the initial baseline measurements. If procedure is performed <30 days from the initial baseline measurements, the TEG measurements must be repeated but the other baseline measurements may be repeated per standard of care at the treating hospital.
- Record protocol specified medications
- Record concomitant medications
- DSA imaging for final aneurysm measurements
- mRS assessment to be carried out by certified independent assessor at the site
- NIHSS
- Assessment of Adverse events of interest

9.5. Procedure

Eligible subjects will be treated with the Pipeline™ Vantage Device per the IFU. During the procedure, Heparin should be administered as an anticoagulation agent.

Note: The Investigator(s) should review and understand the complete CIP and IFU prior to performing any study implant placement in this clinical study.

During or after the procedure, the following data shall be collected and recorded in the eCRF:

- Procedure date and time
- Primary interventionalist first and last name
- Target aneurysm location and dimensions
- Study device placement and resheathing information
- Device implant success (yes/no)- per device used
- Technical procedural success (per subject)
- Subject's radiation exposure (dose and fluoroscopy time)*
- Volume of contrast used
- Post-Pipeline™ Vantage Device implant aneurysm occlusion, device placement and aneurysm status
- Procedural Complications
- Record protocol specified anticoagulation medications
- Record protocol specified DAPT
- ACT: Record at the start, after heparin is given, and at the end of the procedure if collected per standard of care
- Concomitant medications

*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.

Medications appropriate for general anesthesia will be administered using standard hospital practice. Capture all peri-procedural medications specific to the endovascular study procedure (e.g., anti-

hypertensives, prophylactic antibiotics) on the eCRFs. Anesthetics and other standard of care medications for surgical procedures (e.g., saline, povidone-iodine antiseptic, etc.) do not need to be collected.

Medications during treatment:

Anesthetics: The subject will undergo the Pipeline™ Vantage placement under general anesthesia. Medications appropriate for general anesthesia will be administered using standard hospital practice. These are not required to be collected.

Anticoagulants: Heparin use will be required during Pipeline™ Vantage placement with confirmation of anticoagulation via activated clotting time (ACT) prior to insertion of Pipeline™ Vantage. During the procedure, ACT values should be monitored per standard practice and heparin dose adjusted, as clinically appropriate. Heparin may be used up to 24 hours after procedure. If medically indicated, heparin use may be continued after 24 hours, but the Investigator must document the reason for the continued use. Heparin use (dose in ug/dl), frequency, start and stop dates will be collected. ACT values at the start of procedure, during procedure and at the end of procedure will be collected per standard of care.

Other Procedural Medications: Any anti-thrombotic agents e.g., GPIIb3a inhibitors, Bivalirudin, Calcium Channel Blockers, Vasodilators, Antibiotics administered during the procedure shall be collected with their reason for use (prophylactic or for an AE intervention).

9.5.1. Ancillary Devices

Ancillary devices that may be required for the study procedure include, but are not limited to, access devices, 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.

The Pipeline™ Vantage implant is designed to be delivered through a compatible microcatheter of either 0.021 inch (0.53 mm) or 0.027 inch (0.69 mm) inside diameter and minimum 135 cm in length. Compatibility testing with the Phenom™ 0.021" and 0.027" Microcatheter has been performed. Any compatible 0.021" and 0.027" microcatheter may be used but Phenom™ Microcatheter is recommended. Refer to the below table (**Table 9-2**) for microcatheter compatibility for each device size.

Table 9-2. Size ranges: Pipeline™ Vantage Embolization Device with Shield Technology™

Labeled Diameter (mm)	Compatible catheter inner diameter
2.50	0.021 inch (0.53 mm)
2.75	
3.00	

3.25	
3.50	0.021 inch (0.53 mm) or 0.027 inch (0.69 mm) per product label
4.00	0.027 inch (0.69 mm)
4.50	
5.00	
5.50	
6.00	

Ancillary Device Instructions: All endovascular devices are to be used in accordance with directions for use in the package insert approved by the FDA.

The use of guide catheters and microcatheters will be documented in the eCRFs.

9.5.2. Usage of Multiple Pipeline™ Vantage Devices

Based on aneurysm and anatomical factors, if an investigator determines that multiple devices are required to cover the aneurysm neck adequately, an investigator may choose to deploy a maximum of 3 Pipeline™ Vantage Devices that may be stacked at any point in the arterial vessel.

9.5.3. Adjunctive Device Use

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

Adjunctive device use (e.g. coils) is not allowed during the index procedure. Subjects that will require concomitant coiling should be excluded from the study (exclusion criteria). However, previous coiling failed subjects can be included.

9.5.4. Day 0 Imaging

At the beginning of the procedure prior to implantation, the following images shall be collected:

- 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

At the end of the procedure after implantation, the following images shall be collected:

- 3D 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

The Investigator or delegated study staff will submit procedural images to the core laboratory. The Investigator or delegated study staff will ensure that subject identifiers are removed from all submitted images. Image files/CDs should be labeled with the subject's study ID number.

9.5.5. Screen Failure

Subjects that are consented/enrolled in the study but do not undergo Pipeline™ Vantage device implant attempt *i.e.,* puncture at the arterial access site (for not meeting eligibility criteria) should be exited from the study with the reason for exit recorded on eCRFs. Baseline CRFs should also be recorded for Screen Failure subjects.

9.5.6. No Treatment of an Eligible Subject with the Pipeline™ Vantage Device

In the event that the subject was confirmed to be eligible for the study at baseline, signed informed consent, but the target intracranial aneurysm is not treated with the Pipeline™ Vantage Device at the initially scheduled procedure, the subject may be brought in later to undergo the Pipeline™ Vantage Device. In this case:

1) In the event the subject does not meet protocol specified PRU value range (≥60 and ≤200) or TEG value range (>30% to <90%) on the day of the procedure, the procedure should be delayed (and no puncture at the arterial access site performed) until a protocol specified therapeutic range for PRU/TEG is achieved. The day of the puncture at the arterial access site is considered day 0.

2) In cases where PRU/TEG criteria is met and puncture at the arterial access site is performed, and the aneurysm is not able to be accessed or a study device unable to be deployed, the reasons of the inaccessibility of the aneurysm or study device failing to deploy (incomplete treatment) will be captured. Any alternate treatments if received will be captured. Such subjects will not be included in the per-protocol analysis. In cases where the subject is brought back at a later time and undergoes a second procedure with the study device, the date of the first intervention will be considered Day 0. The second intervention (if successful) will not be considered a retreatment. The subject must be brought back for the second intervention within 6 weeks of the initial attempted treatment.

9.6. Post-Placement Antiplatelet Agents

The subject should be tested for antiplatelet response per standard of care and the appropriate dose of antiplatelet agents will be given after the Pipeline™ Vantage Device implant procedure as defined below.

- **Aspirin:** At least 81 mg daily for a minimum of 6 months
- **$P2Y_{12}$ Platelet Inhibitor:** Daily for a minimum of 3 months. Only the following agents shall be utilized:

  Clopidogrel: At least 75 mg daily for a minimum of 3 months

  In situations where patients are hypo-responders to Clopidogrel:

  - **Prasugrel** (Only for subjects <75 years of age and should not be used in subjects with a history of TIA or stroke): 5-10 mg once daily for a minimum of 3 months

  Or

  - **Ticagrelor:** 60-90 mg twice daily with a maximum daily dose of Aspirin not exceeding 100 mg for a minimum of 3 months

Note: Treating physicians should evaluate extending the DAPT regimen based on individual subject condition and response (per their standard of care) Dosing amount will be collected on eCRFs.

9.7. Discharge Exam

At day 7 or discharge (whichever is earlier), the following study assessments shall be performed:

- Record protocol specified medications
- Record concomitant medications
- mRS to be carried out by a certified independent assessor at site
- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- Assessment of Adverse events

Subject discharge disposition will be documented in the eCRFs.

9.8. Retreatment

At the Investigator's discretion, the target aneurysm may be retreated at any time during the study. The retreatment procedure can include any endovascular or surgical intervention including the implant of the Pipeline™ Vantage Device. In such situations, the date that the subject receives the initial Pipeline™ Vantage Device implant (and not the date of the retreatment) will be considered Day 0.

Reason(s) for retreatment of aneurysm shall be documented:

- Device Movement
    - Foreshortening (Peri-procedural or Delayed)
    - Migration
- Aneurysm Growth
- Aneurysm Rupture
- Aneurysm Non-Occlusion
- Insufficient Neck Coverage

Type of Retreatment will be documented:

- Planned
- Unplanned

A retreatment will be considered an "Unscheduled Visit" and subjects will be required to undergo the following study assessments:

- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- Record concomitant and protocol-specified medications
- Imaging (per standard of care)
- NIHSS
- mRS assessment to be carried out by a certified independent assessor at site
- Assessment of Adverse events

Data will be collected for all retreatment procedures in the Retreatment eCRFs. Retreatments should be reported as an SAE.

9.9. Follow-up Evaluations

Subjects that consented/enrolled and underwent a successful Pipeline™ Vantage Device implant will undergo in-clinic follow-up at 30 days, 180 days, 1 year, 2 years, and 3 years. Subjects that had a Pipeline™ Vantage device attempt but were not successfully implanted with the Pipeline™ Vantage device at the index procedure or subsequent attempts, will undergo in-clinic follow-up at 1 year.

9.9.1. 30-Day

At day 30 post-procedure (±7 days), the following study assessments shall be performed and recorded in the eCRFs:

- Record protocol specified medications
- Record concomitant medications
- mRS assessment to be carried out by a certified independent assessor at site
- Full Neurological Exam and assessment of aneurysm symptoms (new, improved, worsened, stable)
- Assessment of Adverse events of interest

9.9.2. 180-Day

At day 180 post-procedure (±30 days), the following study assessments shall be performed and recorded in the eCRFs:

- Record protocol specified medications
- Record concomitant medications
- DSA imaging, if done per standard of care; if DSA not performed per standard of care, subject must undergo CTA imaging.
- mRS assessment to be carried out by a certified independent assessor at site
- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- Assessment of Adverse events of interest

9.9.3. 1-Year

At 1-year post-procedure (±56 days), the following study assessments shall be performed and recorded in the eCRFs:

- Pregnancy test (Pregnancy test (serum or urine) only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test)
- Record protocol specified medications
- Record concomitant medications
- DSA imaging
- mRS assessment to be carried out by a certified independent assessor at site
- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- NIHSS
- Assessment of Adverse events of interest

9.9.4. 2-Year

At 2-year post-procedure (±56 days), the following study assessments shall be performed and recorded in the eCRFs:

- Pregnancy test (Pregnancy test (serum or urine) only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test). At the 2-year follow-up, pregnancy test is only required for female subjects of childbearing potential that are undergoing DSA imaging.
- Record protocol specified medications
- Record concomitant medications
- If aneurysm is not occluded at 1 year or subsequent follow-up visits (per core lab assessment), DSA must be performed at 2-year follow-up. If child bearing potential woman becomes pregnant during the study, subject may obtain MRA without contrast instead of DSA.
- mRS assessment to be carried out by a certified independent assessor at site

- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- Assessment of Adverse events of interest

9.9.5. 3-Year

At 3-year post-procedure (±56 days), the following study assessments shall be performed and recorded in the eCRFs:

- Pregnancy test (Pregnancy test (serum or urine) only required for females of childbearing potential. Females who are surgically sterile or post-menopausal are not required to take a pregnancy test). At the 3-year follow-up, pregnancy test is only required for female subjects of childbearing potential that are undergoing DSA imaging.
- Record protocol specified medications
- Record concomitant medications
- If aneurysm is not occluded at 1 year and subsequent follow-up visits (per core lab assessment), DSA must be performed at 3- year follow-up. Subjects with aneurysm occluded at 1 year and subsequent follow-up visits (per core lab assessment) to undergo DSA, if performed per standard of care; if DSA not collected per standard of care, subject must undergo CTA imaging. Under certain conditions, MRA imaging may be obtained instead of a DSA or CTA imaging e.g., subjects with iodine allergies, borderline renal function, pregnancy, or concerns over excessive radiation. The justification for using MRA over DSA or CTA should be captured in the case report form. Precaution: DSA or CTA imaging are preferred over MRA imaging due to the risk of reduced image quality (artifact) when attempting to visualize near or inside the implanted device with MRA imaging.
- mRS assessment to be carried out by a certified independent assessor at site
- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- Assessment of Adverse events of interest

9.9.6. Unscheduled Visits

At unscheduled follow-up visit (any visit to the study site that is performed between the planned follow-up visits) that occurs post-procedure through the 3-year visit, the following study assessments shall be performed and recorded in the eCRFs:

- Record protocol specified medications
- Record concomitant medications
- DSA imaging (collected if performed per standard of care)
- Imaging of the treated aneurysm using CTA/MRA (collected if conducted per standard of care)
- mRS (for stroke events, mRS should be performed at a minimum of 90 days post event) assessment to be carried out by a certified independent assessor at site
- NIHSS (For stroke events, NIHSS should be performed at the time of event and 24 hours after event)*
- Full neurological exam and assessment of aneurysm symptoms (new, worsened, improved, stable)
- Assessment of Adverse events of interest

*Note that for assessments not performed at study center, the medical charts need to be obtained and sent to Sponsor for CEC evaluation.

9.10. Assessment of Effectiveness

The methods and timing for assessing effectiveness parameters is seen in **Table 9-1**.

9.11. Assessment of Safety

The methods and timing for assessing safety parameters, including adverse events, is seen in **Table 9-1**.

9.12. New Information

Study subjects will be informed of new information that becomes available during the course of this study by their treating physician. Subjects will be notified, at a minimum, in accordance with the procedure of IRB/REB for providing updated information to clinical study subjects.

9.13. Recording Data

Study data will be collected using electronic case report forms and a 21 CFR Part 11-compliant electronic data capture system. The system allows the capability of data collection remotely through the internet so the participating clinical site personnel may log on to the system securely and enter the data. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical

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

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

9.14. Deviation Handling

A protocol deviation is defined as an event where the Investigator or clinical study personnel did not conduct the study according to the clinical protocol. Protocol deviations will be reported to the Sponsor within the eCRF regardless of whether it was medically justifiable or taken to protect the subject in an emergency.

Except under emergency circumstances to protect the rights, safety and well-being of human subjects, the clinical protocol will be followed as described. Subject-specific protocol deviations and non-subject-specific protocol deviations must be reported. Investigators will also adhere to procedures for reporting protocol deviations to their IRB/REB in accordance with their specific IRB/REB reporting policies, timelines, and procedures.

The Sponsor is responsible for analyzing deviations and assessing their significance. Protocol deviations will be routinely reviewed by the Sponsor study team. Where deviations occur, clinical sites are expected to implement preventative and corrective actions to prevent further protocol deviations. Clinical sites with a high rate of protocol deviations will be closely evaluated. If a clinical site demonstrates persistent protocol deviations, the clinical site may be prohibited from enrolling additional subjects, and in some cases, sponsor may terminate the Investigator's participation in the study. If a study required assessment is missed, then it will be considered as a protocol deviation.

9.15. Subject Withdrawal or Discontinuation

Upon completion of the specified study follow-up, the subject will be exempt from further data collection. The subject will be seen by the treating physician according to standard of care following intracranial aneurysm treatment.

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 Principal Investigator or Sponsor for safety or administrative reasons. Subjects that withdraw from the study will not be replaced.

9.15.1. Subject Withdrawal

All enrolled subjects have the right to withdraw their consent at any time during this study. All data collected until the time of subject withdrawal will remain in the study database and will be used for analysis. If a subject is withdrawn from the clinical study, the reason for withdrawal shall be recorded in the eCRF and in the subject's hospital record.

Whenever possible, the clinical site staff should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. If the clinical site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed for the subject and clear documentation of the subject's withdrawal should be provided to the Sponsor.

9.15.2. Subject Discontinuation by Investigator

An Investigator may discontinue a subject from the study, with or without the subject's consent for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject, subject non-compliance, Sponsor decision due to early termination of the study, or if the IRB/REB or regulatory authority stops the study for any reason. If a subject is discontinued from the study, the Investigator will promptly inform the subject and Sponsor.

9.15.3. 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 clinical site must document a minimum of three (3) attempts, and the final documented attempt should be made via registered letter.

10.Risks and Benefits

10.1. Potential Risks

Residual risks from the risk management workbook (RMW15-0012_L) for Pipeline™ Vantage was analyzed to determine the potential clinical harms that may be associated with the use of the Pipeline™ Vantage device. Residual risks, as identified in the risk management work (RMW15-0012_L) 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 Instructions For Use (IFU), (P/N M993912ADOC2). Anticipated Adverse Events and Adverse Device Effects associated with use of the study device and the study procedure(s) include:

Neurological Events of Interest	An event of interest related to the target aneurysm clinical outcome and includes the following events of interest: **Death** Neurological Death **Stroke*** Major Minor **ICH*** **Target Aneurysm Rupture** **Transient Ischemic Attack** **Cerebral Infarction** Symptomatic Asymptomatic **Target Aneurysm Retreatment** Planned Unplanned **Neurological Deficit (decline in mRS)*** Focal Generalized **Visual Symptoms*:** Scintillations Blurred vision Floaters Diplopia Retinal Artery Occlusion Amaurosis Fugax Vision Loss Visual Field Deficit *Ipsilateral Territory: Presumed to be of the vascular origin of the treated vascular territory

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:** Hematoma/hemorrhage Retroperitoneal Localized Pseudoaneurysm (PSA) Vessel occlusion Arteriovenous fistula (AVF) Deep Vein Thrombosis (DVT) Local neurogenic or nerve complications Pain **Vascular Complications (Intra-Cranial or Extra Cranial):** Dissection Perforation Rupture Vasospasms (vasoconstriction) Intracranial fistula formation Occlusion **Thromboembolic Complications** Distal Thromboembolic complication **Anesthesia related complications** Aspiration Hypertension Hypotension **Contrast Related Complications:** Burning Sensation Nausea Contrast Nephropathy Visual Impairment/Visual symptoms **Excessive Radiation Complications:** Skin reddening, Blisters and ulcers, Hair loss (alopecia) Cataracts Late appearing cancers **Systemic complications:** Infection, Shock, Arrhythmia

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 (In-Stent) Stenosis Incomplete Occlusion (At follow-up imaging) Mechanical Device Failures (Device Deficiencies) including but not limited to: ○ Incomplete Open ○ Failure to Open ○ Pushwire Separation issues ○ Loss of Device Integrity (fracture, fragmentation break) ○ Device- Catheter Interaction (excessive friction, trackability issues) ○ Device Foreign Body Reaction (Toxicity, Granuloma) ○ Device Movement ▪ Foreshortening (delayed) ▪ Migration
DAPT Related Events of Interests	Events representing complications of the use of Dual Antiplatelet Therapy. These include fatal or non-fatal, serious or non-serious in nature: Bleeding Complications (GUSTO) ○ Mild ○ Moderate ○ Severe Thrombocytopenia/Thrombotic thrombocytopenic purpura Nose bleeds (epistaxis) Allergic reaction to medications including angioedema Generalized Headache Dizziness Anemia Abnormal Liver and/or kidney function GI Symptoms: ○ Abdominal pain, ○ Nausea, ○ Vomiting ○ Indigestion ○ Gastritis/Gastric Ulcer Dyspnea Fatigue Arrhythmias/ventricular pause(s) Note: For comprehensive potential risks associated with dual antiplatelet therapy, please refer to the most current labelling for the specific antiplatelet drug e.g., Aspirin, Clopidogrel, Prasugrel, Ticagrelor

10.2. Risk Mitigations

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 self-attest to completing a minimum of 20 Pipeline™ Flex Embolization Device cases. All participating investigators have experience conducting clinical research and have adequate personnel to assure compliance to the study protocol.

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. Personally identifying subject information will not be collected on eCRFs or other study-related documentation to be provided to the Sponsor.

In addition, subjects must have pre-procedure $P2Y_{12}$ reaction unit value (PRU) within therapeutic range of 60 and 200 prior to undergoing procedure with the Pipeline™ Vantage Device. Pre-procedure $P2Y_{12}$ reaction unit value (PRU) has shown to predict perioperative thromboembolic and hemorrhagic complications. In a study involving 44 subject and 48 Pipeline™ Embolization Device (PED) procedures for cerebral aneurysm treatment, Delgado Almandoz et al. reported that a pre-procedure PRU value of <60 or >240 (p=0.02) and a technically difficult procedure (p=0.04) were independent predictors of all perioperative thromboembolic and hemorrhagic complications after PED procedures. Inclusion criteria surrounding this optimal pre-procedural PRU value range is intended to minimize subject risk for procedural complications. Additionally, TEG was added for sites OUS where PRU test cannot be performed; based on the TEG test, pre-procedure ADP% between >30% and <90% has been used to evaluate adequate platelet reactivity.[130]

All study data will be monitored by individual site and combined 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 CEC and an independent DMC will provide oversight throughout the trial. 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

Endovascular coiling is a commonly prescribed intracranial aneurysm treatment due to its favorable safety and efficacy profile.[27,131] However, the major limitations of this intracranial aneurysm treatment mode are risks for incomplete occlusion and aneurysm recurrence or recanalization.[132,133] Large and giant complex intracranial aneurysms are even more susceptible to endovascular coiling failure with high rates of incomplete occlusion and subsequent recanalization.[94] Even with the achievement of complete occlusion following coil embolization, lesions are subject to coil compaction leading to recurrence, continued surveillance, and often necessitate retreatment due to rupture risk. Finally, important subgroups of lesions including fusiform, wide-neck, dissecting, and other complex aneurysm configurations are

unsuitable or unsafe for embolization and/or conventional stenting.

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™ 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™ implant addresses the diseased segment of the parent artery, allowing for neoendothelialization to occur, effectively excluding the aneurysm from the vessel wall.[134-136] The occluded aneurysm decreases progressively in size, resulting in a restructuring of the local neurovasculature to its pre-aneurysm state. The curative and permanent outcomes of flow diversion treatment are thus a consequence of three potential mechanisms of action: (i) endovascular reconstruction of a segmentally diseased artery, (ii) flow reduction sufficient to induce thrombosis in the aneurysm sac, and (iii) biologic repair of the aneurysm neck by intimal growth. Finally, because the flow diverter's mechanism of action is independent of aneurysm size, dome-to-neck ratio, or need for dense coil packing, flow diversion strategies seem particularly well-suited to wide-necked and fusiform aneurysms, for which no optimal endovascular and/or surgical alternative exists. 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 trial results and findings from the published literature report Pipeline™ Embolization Device and Pipeline™ Flex Embolization Device technical success rates of 87-100%.[52,57-62,87] Complete aneurysm occlusion is commonly measured using the Raymond Roy Scale.[1] Arteriographic outcomes are divided into three categories in this scale: (1) complete occlusion, (2) residual neck, and (3) residual aneurysm.[1] Pipeline™ Embolization Device treatment achieves up to approximately 95% permanent aneurysm occlusion.[49-55,87] Aneurysm obliteration has been shown to be maintained over long-term follow-up - further evidence of the high probability for patients to experience one or more major benefits following Pipeline™ Embolization Device treatment.

The introduction of the Pipeline™ Vantage Device aims to further improve the safety and effectiveness profile of the device. The Shield Technology™ surface modification, based on phosphorylcholine (PC), aims to improve the biocompatibility and decrease the thrombogenicity of the Pipeline™ Vantage device while preserving the clinically proven design of the Pipeline™ implant. In vivo studies have shown that PC-coated stents implanted in the peripheral arteries inhibit platelet adherence and thrombosis in this specific application.[69,71,72,137] Thus, it is anticipated that the benefits achieved from the Pipeline™ Flex Embolization Device should be at least maintained and perhaps improved with the use of Pipeline™ Vantage Embolization Device with Shield Technology™.

10.4. Risk-Benefit Rationale

The potential risks associated with the use of the Pipeline™ Vantage Device, based on risks observed with the Pipeline™ Embolization Device and Pipeline™ Flex Embolization Device, include ischemic

stroke,[62,61,85,138,139,140,141] intracranial hemorrhage,[52,53,142-146] neurological deficit,[58] and death.[33,50,51,53-55,87,91,130,138,145,147-202]

Ischemic stroke with the Pipeline™ Embolization Device has ranged from 0.96% to 10.7%.[52-54,61,62,85,127,138,169,181,182,184,194,196,203-220] Thirty-three studies reporting clinical outcomes in ≥ 25 patients observed 230 ischemic stroke or cerebral infarction. Five studies did not report rate of ischemic stroke or cerebral infarction.[205,209,212,220] One study reported ischemic stroke in one out of 59 patients.[206] Three studies reported cerebral infarction in one of 50 patients,[220] one of 40 patients,[209] and two of 140 patients.[205] One study reported stroke in two of 110 patients.[212] Overall, three of the studies that reported ischemic stroke reported that the events were procedure-related and one study reported an ischemic stroke that was device related.[154,181,184,221,222] Considered the total patients captured in the relevant literature (9,121), the number of reported ischemic stroke events was low; thus the benefits of the use of the Pipeline™ device are expected to outweigh the risk.

Pipeline™ Embolization Device studies have also reported intracranial hemorrhage (0.6% to 12%).[52,53,84,85,91,139,144,149,152,164,166,182,185,187,203-205,207,211,213,215,216,219,223-235] In their IntrePED sub-analysis, Brinjikji et al. investigated the risk factors for hemorrhagic complications with Pipeline™ Embolization Device treatment.[236] Variables related to higher odds of intraparenchymal hemorrhage included treatment of ruptured aneurysms and use of more than 3 Pipeline™ Embolization Devices.[236] The exact cause of intracranial hemorrhage with Pipeline™ Embolization Device use is unknown but possible explanations include use of DAPT and hemodynamic perturbations from flow diverter treatment.[236]

Pipeline™ Embolization Device studies have also reported Neurological deficit/dysfunction. Thirty-six studies reporting clinical outcomes in ≥ 25 patients observe a total of 145 neurologic deficits/dysfunctions, with rates ranging from 0.3% to 15.4%.[50,53,84,140,152,153,160,169,173,181,187,196,204,211,227,232,237-255] Six studies did not report rates for neurological deficits/dysfunction, but reported the number of cases, totaling 15 reported cases in 271 subjects. The number of reported neurological deficit/dysfunction was low; thus the benefits of the use of the Pipeline™ device are expected to outweigh the risk.

Reported mortality with Pipeline™ Embolization Device use was 0.7% to 11.5% from 24 studies reporting clinical outcomes in ≥ 25 patients.[52,53,85,127,144,149,150,164,169,175,182,187,205,210,213,215,219,224,225,228,229,233] A total of 132 deaths were reported in these studies.[52,53,85,127,144,149,150,164,169,175,182,187,205,210,213,215,219,224,225,228,229,233] When taken into consideration with the rest of the published literature, out of the total patients captured in the literature, the number of reported deaths was low; thus the benefits of the use of Pipeline™ are expected to outweigh the risk.

The risks associated with intracranial aneurysm treatment have to be balanced with the lifetime risk of rupture, patient life expectancy, and patient stress from the knowledge of the aneurysm and the possibility of rupture.[256] When an intracranial aneurysm ruptures, the resulting SAH is life-threatening.

Subarachnoid hemorrhage from an aneurysm rupture is associated with 45% 30 day mortality and of the patients who survive, half experience morbidity.[112,257]

Published data on the Pipeline™ Embolization Device and Pipeline™ Flex Embolization Device support its efficacy and safety in the treatment of small, medium, large, and giant wide-neck aneurysms in both the anterior and posterior circulation.[52,55,59,61,84,85,166,258] The device currently has commercial approval in the US for large and giant wide-neck aneurysms and preliminary evidence with the Pipeline™ Embolization Device has shown that it can safely completely occlude small aneurysms. In a 100 patient study, Chalouhi et al. observed 72% (54/75) of small aneurysms were completely occluded (mean follow-up time: 6.3 months).[166] All patients achieved a favorable outcome at 7.3 month mean follow-up.[136] Griessenhauer et al. treated 52 small paraophthalmic artery aneurysms and noted 81.5% (44/54) complete occlusion with a median follow-up of 11.5 months.[259] There was no mortality or permanent visual deficit.[259] Overall complete occlusion rates ranged from 72-86% at mean follow-ups of 4-6.3 months. Morbidity was 0-5% and mortality was 0-2.3% at mean follow-up of 4-7.3 months.[33,160,166,259,260] Safety data from the IntrePED study reveal that of the 268 patients with unruptured intracranial aneurysms <10 mm located in the ICA up to the terminus, the combined neurological morbidity and mortality rate was 3.4%.[85]

The published literature provides evidence that the risk-benefit ratio of the Pipeline™ Embolization Device and Pipeline™ Flex Embolization Device is acceptable. The clinical benefits achieved with the Pipeline™ Embolization Device and Pipeline™ Flex Embolization Device for the endovascular embolization of intracranial aneurysms is significant and outweighs the individual and overall residual risk associated with its use. Pipeline™ Vantage device should enhance the deliverability; and lower material thrombogenicity associated with the established Pipeline™ Flex Embolization Device based upon analogous thrombotic reductions seen in peripheral stent applications using PC surface modification. In addition, pre-clinical bench and animal testing of the Pipeline™ Vantage Device indicates non-inferiority to the established Pipeline™ Flex Embolization Device.

The Pipeline™ Vantage Device consists of an improved version of the same Pipeline™ Flex Embolization Device implant with increased radiopacity and pore density. The delivery system of Pipeline™ Vantage was designed to be compatible with 0.021" inner diameter micro catheters for select sizes and also includes a new Advanced Resheathing Mechanism with enhanced reliability. Additionally, Pipeline™ Vantage has a phosphorylcholine polymer coating on the implant braid. Pipeline™ Vantage, Pipeline™ Shield, Pipeline™ and Pipeline™ Flex share substantial equivalence in terms of indication for use, structural composition, construction materials, manufacturing process, safety, and performance. In a prospective clinical study, Martinez-Galdamez et al. assessed peri-procedural outcomes and early safety outcomes associated with the use of Pipeline™ Shield for the treatment of unruptured aneurysms in 50 patients.[217] The device was successfully deployed in 98.1% of patients. Complete wall apposition was achieved immediately in 96% patients, with the aneurysm neck successfully covered in all patients. No major strokes or neurologic deaths were reported 30 days post-procedure. Retreatment was not required in any

of the patients. During the 30-day follow-up period, procedure-related, SAEs, including access site hematoma in one (2%) patient, carotid artery dissection in one (2%) patient, cerebral infarction in one (2%) patient, and nausea in two (4%) patients were reported. No morbidity or mortality were reported. Results from this study demonstrate that use of Pipeline™ Flex Embolization Device with Shield Technology™ was not associated with greater risk compared to Pipeline™ and Pipeline™ Flex.

Collectively, based on the extensive data with previous generations of the Pipeline™ device, it is expected that the Pipeline™ Vantage 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 Embolization Device. Therefore, Medtronic considers the potential benefits of the Pipeline™ Vantage Device to outweigh the potential risks in the defined subject population.

11. Adverse Events and Device Deficiencies

All adverse events (AEs) will be collected and evaluated from point of enrollment through study exit per the Schedule of Assessments for all subjects enrolled in the study. Adverse event status will be evaluated throughout 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 IRBs/REBs/Ethics Committees within the specified reporting timeframe per 21 CFR 812 or local regulations. Reported AEs shall be categorized by the site investigator when reporting to the sponsor using the definitions provided in **Section 11.1 and 11.3**.

Target Aneurysm related signs and symptoms that in the opinion of the Investigator existed prior to the point of puncture at the arterial access site on the day of the study procedure (Day 0) are not considered AEs (but will be collected as Medical History/ Risk Factors) 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™ Vantage Device is not made due to ineligibility of the subject for the study (e.g., inability to access the aneurysm or other exclusion criterion identified during the procedure) any adverse events or device deficiencies that occur are to be collected through subject's study exit.

All AEs, as well as their start dates, action taken, severity, causality assessment, seriousness and outcome should be documented in the subject's medical records and in the eCRF.

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

11.1. Adverse Event Definitions

11.1.1. Adverse Event

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. (ISO 14155:2011 3.2)

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

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

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

11.1.2. Serious Adverse Event

Adverse Event that

a) Led to death, injury or permanent impairment to a body structure or a body function

b) Led to a serious deterioration in the health of the subject, that either resulted in:

   a. A life-threatening illness or injury, or

   b. A permanent impairment of a body structure or a body function, or

   c. In-patient hospitalization or prolongation of existing hospitalization, or

   d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011 3.37)

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a SAE.

11.1.3. Adverse Device Event

Adverse event related to the use of an investigational medical device. (ISO 14155:2011 3.1) The investigational medical device for this study is the Pipeline™ Vantage Device used during the study procedure (Day 0).

Note 1: This definition includes any adverse events resulting from insufficiencies or inadequacies in the IFU, the deployment, implantation, installation, operation, or any malfunction of the investigational medical device.

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

11.1.4. Serious Adverse Device Event

Adverse device effect that has resulted in any of the consequences characteristic of a SAE. (ISO 14155:2011 3.36)

11.1.5. Unanticipated Serious Adverse Device Event (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2011 3.42)

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

11.1.6. Unanticipated Adverse Device Event

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. 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 AE should be evaluated according to the following scale:

- 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.

11.1.8. Causality Assessment of Events

The relationship between the occurrence of each adverse event to the following will be assessed:

- Use of the medical device for this study, Pipeline™ Vantage Device
- Index study 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., surgical procedures 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 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 DAPT:

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 event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
   - the event does not depend on a false result given by the investigational device used for diagnosis*, when applicable [*If an investigational device gives an incorrect diagnosis, the subject might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the subject might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition];
   - harms to the subject are not clearly due to use error;
   - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2. Unlikely:

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

3. Possible:

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

4. Probable:

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

5. Causal relationship:

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

   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that:
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on:
   - the adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis*, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

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

An adverse event can be related both to 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. Reporting of Adverse Events

The Investigator is required to report all reportable SAEs and UADE's within 24 hours after first learning of the event to the Sponsor (**Table 11-1**). In addition, where local country regulatory authorities specially require a more stringent definition or additional requirement, the local regulation should also be complied with.

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

The primary method of reporting UADE's is through SAE hotline email.

If the database is unavailable or not accessible the Investigator may send the information to the SAE email hotline.

The Investigator shall provide all requested supporting documentation for reported SAEs or AEs (blinded/de-identified as to subjects' identity) through the SAE Hotline or to the monitor and/or clinical team via email as requested. The Investigator shall complete data entry in the study Electronic Data

Capture (EDC) database with the same information provided on the paper form as soon as the database becomes available.

Table 11-1. Expedited Adverse Event and Device Specific Event Reporting Requirements

SAEs / DD with SADE potential	Investigator will notify Sponsor of all SAEs and Device Deficiencies with SADE potential within 24 hours of being aware of the event.
Primary method of reporting	Corresponding eCRF (e.g., Adverse Event CRF or Device Deficiency CRF) in study EDC database
Sponsor 24 Hour SAE/UADE Hotline contact information:	**Email:** dl.ADVANCESAEHotline@medtronic.com To be used as back-up in event that database if unavailable or inaccessible within required reporting timeline or for reporting all UADE's.

As additional information becomes available, copies of source documentation which contain significant information related to the event such as operative reports, imaging studies, discharge notes and subject summaries etc. may be requested for a complete evaluation of the event by the sponsor or CEC.

In regard to subject deaths, a de-identified copy of the death certificate and a de-identified copy of the autopsy report, if applicable, is to be sent to the Sponsor. Any other source documents related to the death should also be provided to the Sponsor and should be blinded/de-identified as to the subject's identity. In the event that no source documents are available, the Investigator is requested to describe the circumstances of the subject's death in a letter, e-mail or other written communication to the Sponsor.

The Investigators are required to comply with their local Safety reporting requirements per their region/IRB/REB.

UADEs/USADEs have expedited reporting requirements. UADEs must be reported by the Investigator to the Sponsor via email provided above within 24 hours and the reviewing IRB/REB per IRB/REB reporting requirement, but in no event later than 10 working days after the investigational site first learns of the event (CFR 812.150(a)(1)).

11.3. Device Deficiency

Device Deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (ISO 14155:2011 3.15).

Note that device deficiencies include malfunctions, use errors, and inadequate labeling.

All device deficiencies should be reported to the Sponsor on the DD eCRFs in a timely manner.

Device Deficiencies that have the potential to cause a serious adverse device effect shall be reported to the sponsor within 24 hrs of site's awareness of the event.

These should be reported to the local competent authorities and IRBs/REBs 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.

All Qualified Investigators must report product complaints to the sponsor (i.e., any Medtronic personnel) and Health Canada as required by governing law (i.e., Canada Medical Device Regulations 1998 (SOR/98-282).

12. Data Review Committees

To avoid and minimize bias, an independent CEC, Imaging Core Laboratory, and DMC will be in place to assess adverse events, occlusion and parent artery stenosis, and oversee the safety of the trial respectively.

12.1. Clinical Events Committee

A CEC shall be comprised of a minimum of three (3) physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study and will be responsible for an independent, objective and consistent review of AEs.

Event level adjudications will be performed by a single CEC member for start and stop dates, seriousness, causality assessment, severity and outcomes for all adjudicable adverse events per CEC charter.

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 potential imaging obtained in support of the adverse event to assist with adjudication.

12.2. Imaging Core Laboratory

To objectively and consistently assess imaging data, an imaging protocol will be provided to the site. The imaging core laboratory will be responsible for the qualitative image analysis to determine aneurysm occlusion, parent artery stenosis, and discernible device movement.

12.2.1. Screening Eligibility Review

The core lab will be responsible for review of screening images to determine suitability for treatment in the study. In this role, the core lab will perform measurements to confirm the anatomical dimensions included in the eligibility criteria.

The reviewing committee (Physician Screening Committee) will be responsible for determining subject eligibility in the study. Further details on the Physician Screening Committee will be provided in the core lab charter.

12.2.2. Pre-Procedure Anatomy

Baseline imaging will be reviewed to assess baseline aneurysm and parent artery characteristics.

12.2.3. Aneurysm Occlusion

Post-procedure and follow-up angiograms will be reviewed to assess aneurysm occlusion according to the Raymond Roy Scale[1] (**Figure 12-1**).

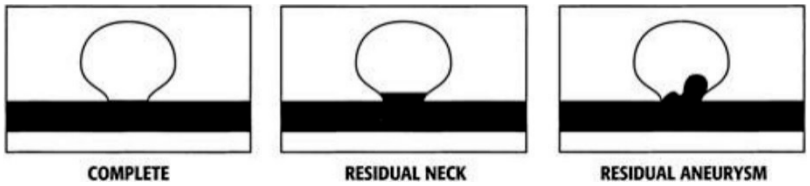


Figure 12-1. Raymond Roy Scale for Grading Aneurysm Occlusion

- **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

12.2.4. Parent Artery Stenosis

Post-procedure angiograms will be reviewed to assess stenosis in the parent artery across the entire Pipeline™ Vantage Device implant. Vessel stenosis will be measured and judged according to the scale in **Table 12-1** in cases, where paired imaging is available for DSA. If DSA is unavailable, flow limiting stenosis (> 50%) vs. non-flow limiting stenosis (≤50%) will be assessed by CTA images.

Table 12-1. Stenosis Grading Scale

Category	Degree of Stenosis
0	1–25%
1	>25 – ≤50%
2	>50 – ≤75%
3	>75–100%

12.3. Data Monitoring Committee

The DMC will be an independent group that will serve as a data monitoring committee. The DMC will be comprised of representatives from multiple disciplines including but not limited to neurology,

biostatistics/epidemiology, neurosurgery and interventional neuroradiology that are independent of the clinical sites.

In the safety monitoring role, this board shall provide recommendations to the Sponsor regarding in the conduct of the clinical study. The DMC will establish proposed safety monitoring criteria for the study and will establish and document any required analysis time points for assessing safety. The group will also establish a DMC Charter which will describe the DMC operating procedures.

13. Statistical Design and Methods

13.1. General Principles

A detailed statistical analysis plan (SAP) will be finalized prior to performing any analyses to expand upon the statistical methods presented below. Summary tables will summarize data for all subjects combined. All recorded data will be presented in the individual data listings sorted by site patient, and date of observation.

13.2. Sample Size Determination

The target sample size for this clinical investigation is 100 patients enrolled and treated and followed for safety events with the expectation of having digital imagery at 1-year post-procedure on a minimum of 80 patients.

Sample size estimation for the primary safety endpoint was initially based on recommendations by the FDA considering the precision of the estimates. For the primary safety endpoint, the incidence of major stroke in the territory supplied by the treated artery or neurological death at 1 year, with an incidence as high as 8%, a sample size of 100 subjects will provide a precision of approximately ± 5.5%, which is considered to be reasonable.

The basis for establishing the a priori threshold for the primary safety endpoint at 14% is rooted in the derivations presented in the table presented below, predicated on a population for analysis of 100 patients (with up to 140 subjects enrolled). Simulations were prepared in SAS assuming an observed incidence in the ADVANCE IDE study of primary safety events ranging from 5.6% to 6.9%. Scenarios 1 through 9 reveal a power greater than 80% (**Table 13-1**).

Table 13-1. Estimated Power Over a Range of Possible Primary Safety Outcomes with 100 Patients (a priori threshold of 14%)

Simulation Scenario	a priori Threshold (proportion)	Observed Incidence (proportion)	Actual Type 1 Error Rate	Power (percent)
1	0.14	0.0560	0.0492	89.19
2	0.14	0.0570	0.0492	88.29
3	0.14	0.0580	0.0492	87.36
4	0.14	0.0590	0.0492	86.38
5	0.14	0.0600	0.0492	85.37
6	0.14	0.0610	0.0492	84.32
7	0.14	0.0620	0.0492	83.23
8	0.14	0.0630	0.0492	82.11
9	0.14	0.0640	0.0492	80.96

10	0.14	0.0650	0.0492	79.77
11	0.14	0.0660	0.0492	78.55
12	0.14	0.0670	0.0492	77.30
13	0.14	0.0680	0.0492	76.02
14	0.14	0.0690	0.0492	74.72

Although the power is less than 80 when the incidence of safety events is 6.5% or higher, the power is still adequate when contrasted against the actual upper bound of the 1-sided 97.5% exact binomial confidence interval. Specifically, if 7 of the 100 patients experience a primary safety event, the upper bound of the 1-sided 97.5% exact binomial confidence interval would be 13.89% and below the 14% threshold.

For the primary effectiveness endpoint, the power was estimated for an observed rate between 65% to 80% considering sample sizes from 80 to 100 patients. With a type 1 error rate of 2.5%, 100 patients would have 82.8% power to reject the null hypothesis if the observed incidence of complete aneurysm occlusion without parent artery stenosis was 65%. Under the same scenario with 80 patients, the power would be 83.5% if the observed incidence of complete aneurysm occlusion without parent artery stenosis was 67%. To ensure at least 95% power with 80 and 100 patients, the observed incidence of complete aneurysm occlusion without parent artery stenosis or retreatment would need to be a minimum of 71% and 69%, respectively. Requiring a minimum sample size of 100 patients with 95% power translates into a minimum incidence of complete aneurysm occlusion without parent artery stenosis of 69% which is in-line with the previous results with the results from previous Pipeline studies.

13.3. Analysis Populations

To ensure adequate representation patient with large and giant aneurysms must be enrolled. All primary and secondary endpoints will be analyzed both on an ITT and PP basis. All summarizations and tabulations will be conducted on the ITT population, defined below.

Intent-To-Treat Population: All subjects who were consented and in whom deployment of the Pipeline™ Vantage Device was attempted (i.e., puncture at the arterial access site), independent of the procedure being completed successfully.

Subject will not be considered part of the ITT population if the puncture at the arterial access site for deployment of Pipeline™ Vantage Device was not successful. If the puncture at the arterial access site for deployment of Pipeline™ Vantage Device was successful, the subject will be considered part of the ITT population. Consented subjects who withdraw consent prior to undergoing the study procedure or are found not to meet the inclusion/exclusion criteria prior to undergoing the study procedure, will not be included in the ITT population.

The ITT population will be the primary population for all analyses.

The PP population defined below will be used for sensitivity analyses and to provide outcomes for subjects with observed data.

Per-Protocol Population: Per-protocol population is ITT subjects excluding the following subjects:

- Subjects with use of more than 1 treatment device (e.g., coils) other than Pipeline™ Vantage device during index procedure
- Subjects with failed implantation of study device at index procedure
- Subjects assessed as mRS ≥3 at baseline by independent and certified assessors

13.4. Eligibility of Subjects, Exclusions, and Missing Data

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.

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

The primary presentation of the results for the ITT population will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. This procedure uses an iterative modeling approach to generate estimates for patients who withdraw prematurely, incorporating multivariate imputation by fully conditional specification (FCS) methods. The discriminant function method will be used for classification variables. With the function method of classification, the missing values will be imputed sequentially in the following order: age, gender, aneurysm diameter and location (ICA: yes or no). Additional sensitivity analyses will also be conducted using the last observation and the post-procedure observation carried forward. A tipping point analysis will also be conducted.

Rules for imputing a full date for interventions with incomplete or missing start-dates will be addressed in detail in the Statistical Analysis Plan.

13.5. Justification of Pooling

This study will be powered statistically based on the primary efficacy and safety endpoint. To assess poolability of the data across study sites and other predefined factors that may affect outcome, a threshold of 0.10 will be used. The testing strategy and exact model for analysis will be included in the Statistical Analysis Plan (SAP). In summary, a generalized linear model will be used, specifying the dependent variable as dichotomous and the distribution as binomial. The exact location of the aneurysm will be included in the class statement, provided each location has ≥2 patients. Aneurysm size will be introduced into the model as a continuous variable. Separately, aneurysm size will be examined around prespecified thresholds to determine if location is a significant predictor of outcome. If clinical site, or any predefined factor is found to be a significant predictor of outcome ($p<0.1$), the factor will be retained

in the model and adjusted confidence intervals will be derived as a secondary examination of the primary endpoint.

Small clinical sites (i.e., clinical sites that have less than 4 patients) will be identified and the following method will be used for combining the data. Data from all small clinical sites will be combined to form a single clinical site in the evaluation of clinical site interaction effects. Once combined, the pooled clinical site will remain as such for all analyses for which a clinical site interaction effect is determined. If the pooled smaller clinical sites represent a single clinical site that has more than twice as many patients as the largest single clinical site, however less than 3 times as many patients, the small clinical sites will be ranked by size and then by clinical site number and divided into 2 pooled assignments using an alternating treatment sequence (ABABAB). If the pooled smaller clinical sites represent a clinical site that has more than three times as many patients as the largest single clinical site, however less than 4 times as many patients, the small clinical sites will be ranked by size and divided into 3 pooled assignments using an alternating treatment sequence (ABCABCABC). This methodology will be applied, based on the initial pooling of the smaller clinical sites. If the pooling of smaller clinical sites results in a pooled clinical site that still has less than 4 patients, the smallest clinical site that was not included in the pooling procedure will be included and the procedure repeated.

13.6. Subgroup Analysis

Sub-group analysis will be performed based on aneurysm location and size. Note that the subgroup analyses listed here are not independently powered and they are for exploratory purpose only. Statistical testing analogous to the above (Section 13.5) will be performed to assess poolability of these subgroups into the overall study results. The incidence for the primary efficacy and primary safety endpoints will be derived and summarized without adjustment for other factors. A secondary examination will be performed where aneurysm location and aneurysm size will serve as covariates in an adjusted model. It is indeterminate if there will be sufficient power to discriminate across these 2 factors, given the enrollment into the study will not be controlled for either factor. A series of derived estimates will be generated for the primary efficacy and safety endpoints retaining aneurysm size and anatomical location as a secondary examination of the primary endpoint. All factors and method of analysis will be clearly defined in the SAP.

13.7. Interim Analysis

No formal interim analyses are planned for the purpose of stopping this trial early for effectiveness.

13.8. Statistical Analysis

All statistical analyses will be done using the SAS System software, version 9.4 or later (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

13.8.1. Demographics, Clinical Baseline and Procedure Characteristics

Patient demographics, clinical history, risk factors, aneurysm characteristics, procedure characteristics, and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and frequency tables for discrete variables.

13.8.2. Primary Endpoint Analysis

13.8.2.1. Primary Effectiveness Endpoint

The pre-specified threshold of 50% for effectiveness endpoint is based on the effectiveness threshold of the recent PREMIER study with the Pipeline™ Device. This threshold must be exceeded at a certain magnitude to reject the null hypothesis and merely serves a statistical boundary for analysis. If the upper bound of the 1-sided 97.5% exact binomial confidence interval is >50%, the primary effectiveness endpoint will have been met.

To ensure at least 95% power with 80 and 100 patients, the observed incidence of complete aneurysm occlusion without parent artery stenosis or retreatment would need to be a minimum of 71% and 69%, respectively. Requiring a minimum sample size of 100 patients with 95% power translates into a minimum incidence of complete aneurysm occlusion without parent artery stenosis of 69% which is relatively in-line with the previous results with the results from previous Pipeline studies.

The primary effectiveness endpoint is the incidence of complete aneurysm occlusion (Raymond Roy Scale Class 1) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm at 1-year post-procedure. The incidence will be summarized using counts and percentages; the 1-sided upper bound of the 97.5% confidence limit for the incidence will be evaluated relative to the a priori threshold of 50%. The hypothesis for evaluating the primary effectiveness endpoint is stated below:

H_o: Incidence at 1-year post-procedure of complete aneurysm occlusion without retreatment or significant parent artery stenosis is ≤ 50.0%

H_a: Incidence at 1-year post-procedure of complete aneurysm occlusion without retreatment or significant parent artery stenosis is > 50.0%

If the upper bound of the 1-sided 97.5% exact binomial confidence interval is >50%, the primary effectiveness endpoint will have been met.

All eligible patients will undergo follow-up at 12 months.

13.8.2.2. Primary Safety Endpoint

The primary safety endpoint is 1-year incidence of major stroke in the territory supplied by the treated artery or neurological death. The incidence will be summarized using counts and percentages; the 1-sided

upper bound of the 97.5% confidence limit for the incidence will be evaluated relative to the a priori safety threshold of 14%. Given the primary safety endpoint reported in PMA P100018 was 5.6%, an incidence of ≤7% for the primary safety endpoint would be considered clinically acceptable within the confines of a study of this general size. The hypothesis for evaluating the primary safety endpoint will be evaluated according to the following 2 requirements:

Requirement 1: The incidence of primary safety events must be ≤7%, and

Requirement 2: The null hypothesis must be rejected in favor of the alternative:

H_o: Incidence at 1-year post-procedure of major stroke and/or neurological death is ≥ 14.0%

H_a: Incidence at 1-year post-procedure of major stroke and/or neurological death is < 14.0%

If the incidence of primary safety events is ≤7% and the upper bound of the 1-sided 97.5% exact binomial confidence interval is <14%, the primary safety endpoint will have been met.

All eligible patients will undergo follow-up at 12 months.

13.8.3. Secondary Endpoint Analysis

All the secondary endpoints will be summarized using frequency tables presenting counts and percentages; no statistical testing will be performed against any preset thresholds for the secondary endpoints. The secondary endpoints include the following:

The following will be assessed for the effectiveness outcome measures:

1. Incidence of successful device implantation at the target site
2. Incidence of complete aneurysm occlusion (Raymond Roy Class 1) at 1- and 3-years post-procedure
3. Incidence of target aneurysm recurrence at 1- and 3-years post-procedure

The following will be assessed for the secondary safety endpoints:

1. Incidence of major stroke in the territory supplied by the treated artery or neurological death at 2- and 3-years post-procedure
2. Incidence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure
3. Incidence of delayed intraparenchymal hemorrhage >30 days post-procedure through 1-year post-procedure

4. Incidence of subjects with disabling strokes that have a mRS decline to a score of 3 or more (mRS ≥ 3) due to a stroke-related cause assessed at a minimum of 90 days post-stroke event at 1 year, 2 year, and 3 year post-procedure

13.8.4. Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activity (MedDRA) system dictionary.

CEC adjudicated data Tables to summarize the incidence rates will be created for each of the following groups: (At 1 year, 1- 2 years, and 2- 3 years)

- Adverse events (non-Serious) related to intervention (Procedure, anti-platelet therapy (APT)), Causal, Probable
- Serious adverse events related to Intervention (Procedure, APT)- Causal, Probable
- Adverse device effects (Non-SAE Related to Study Device- causal, probable)
- Serious adverse device effects (SAE Related to Study Device- causal, probable)
- Unanticipated serious adverse device effects (USADE)/UADE
- Adverse events by severity (Mild, Moderate and Severe) related to Device, Procedure or APT (causal, probable)

14. Ethics

14.1. Statement(s) of Compliance

This clinical study will be conducted in compliance with 21 CFR 812, Canada Medical Device Regulations 1998 (SOR/98-282), the latest version of the Declaration of Helsinki, laws and regional or national regulations of the countries in which the clinical study is conducted, including but not limited to local good clinical practice, data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

All principles of the Declaration of Helsinki will be implemented in this clinical study by means of the informed consent process, IRB/REB approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment, publication policy, etc.

The Sponsor will avoid improper influence on, or inducement of the subject, monitor, and Investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements, or IRB/REB approval.

14.2. Institutional Review Boards/Research Ethics Board

The Sponsor and/or Investigator must submit this clinical protocol, subject Informed Consent Form and Investigator's Brochure to the appropriate Institutional Review Board (IRB)/Research Ethics Board (REB) and is required to forward to the Sponsor a copy of the written and dated approval.
The study (study number, clinical protocol title, and version), documents reviewed (e.g. clinical protocol, ICF, etc.) and the date of the review should be clearly stated on the written IRB/REB approval. In addition, the approval letter needs to be accompanied by an IRB/REB roster, letter of compliance, or other documentation to allow verification that the Investigator, other investigation site personnel, and/or Sponsor personnel are not members of the IRB/REB. If they are members of the IRB/REB, written documentation is required stating that he/she did not participate in the approval process.
The study will not start at a clinical site and subjects will not be enrolled until a copy of written and dated IRB/REB approval has been received by the Sponsor.
Any amendment or modification to the clinical protocol must be sent to the IRB/REB. The IRB/REB must also be informed of any event likely to affect the safety of subjects or the conduct of the study.
If the IRB/REB imposes any additional requirements (e.g. safety reports, progress reports etc.), this will be followed, if appropriate. The Sponsor will prepare the required documents and send them to the Investigator for reporting to the IRB/REB. Investigators must inform the Sponsor of any change in status of the IRB/REB approval. If any action is taken by an IRB/REB with respect to the investigation, that information will be forwarded to the Sponsor by the respective Investigator.

The Informed Consent Form used by the Investigator for obtaining the subjects informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/REB for approval.

15. Study Administration

15.1. Steering Committee

A Steering Committee will oversee the conduct and scientific aspects of the study. A Steering Committee comprised of 1 chair and 4 study investigators knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study will be responsible for providing expert medical guidance in the following roles:

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

15.2. Clinical Site Selection

The ADVANCE IDE will be conducted at up to 30 sites, including up to 25 sites in U.S. and up to 5 sites OUS.

The Sponsor or representative of the Sponsor will assess each potential clinical site to ensure the Principal Investigator and his/her staff has the facilities and expertise required for the study. Clinical sites will be selected based upon a clinical site assessment, appropriate facilities, and the qualifications of the Investigator(s). Individual Investigators will be evaluated by the Sponsor based on experience with the intended procedure(s) and ability to conduct the study according to the clinical protocol.

To participate, a clinical site must have the following:

- Previous experience with clinical research
- Commitment from the investigator to enroll only subjects meeting the study criteria
- A study coordinator or study team member who can enter data and respond to queries
- Willingness to adhere to all relevant Core Laboratory requirements
- Willingness to perform necessary documentation (e.g., eCRF)
- Willingness to sign and adhere to the Investigator Statement
- Willingness to participate in investigator meetings as scheduled by Medtronic
- Willingness to provide full access to subject electronic medical records, or to provide complete, certified copies of subject records for the duration of the subject's study participation

Medtronic will maintain an updated list of principal investigators, investigation sites and associated IRBs/REBs, institutions and their scope of duties in the Trial Master File.

15.3. Monitoring

Medtronic, as the Sponsor, will be responsible for ensuring that adequate monitoring at each clinical site is completed to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted in compliance with applicable regulations. Appropriately qualified and trained personnel appointed by the Sponsor will conduct monitoring at each clinical site at the start, during and at the closure of the clinical study per the Medtronic Standard Operating Procedures (SOPs) and the Clinical Monitoring Plan. Monitors for the clinical study will consist of Sponsor clinical staff and/or qualified contract services (e.g., CRO) appointed by the Sponsor. The primary contact for the clinical study will be the Clinical Study Manager and monitoring (Refer to the contact list).

Study Monitors will conduct clinical site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, investigational device accountability, compliance with applicable laws and regulations, compliance with the clinical protocol, compliance with the signed investigator agreement, and compliance with IRB/REB conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the Principal Investigator/site staff is cause for the Sponsor to put the Investigator/site staff on probation or withdraw the Investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

All subject treatment, follow-up visits and phone conversations/interviews will be fully documented either on the source document or in the subject's medical records. Information entered into the eCRFs will be verified against the source documents and subject's medical records according to the monitoring plan. Additional subject medical record review may be required for AE adjudication. Source documents may be photocopied if required. The study Monitor will also check the Investigator Site File (ISF) to ensure that all study-related documents are current.

Medtronic representatives or their agents may be present during the endovascular procedure.

15.3.1. Direct Access to Source Data/Documents

By participating in this research study, the Investigator agrees to permit monitoring and auditing by the Sponsor and/or its designee(s) and inspection by applicable regulatory authorities. The Investigator also agrees to allow the Sponsors CRAs/monitors/auditors/FDA investigators to have direct access to his/her original research-related study records (e.g. complete medical records, source documentation, and billing information) for review. The Principal Investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Sponsor field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRFs.

15.3.2. Clinical Site Training

Each clinical site will be trained to the investigational plan and any updates if applicable. Investigator/site personnel will undergo training prior to performing any study-related procedures (e.g., at a Site Initiation Visit or training meeting). All training must be documented. Existing clinical site personnel who have been delegated new tasks and new clinical site personnel will undergo training to the investigational plan, as appropriate. Training for Investigators and their site team is dependent on their delegated task(s) per Delegation Task List (DTL) Log. Investigators and their site team are to be trained to perform their delegated responsibilities prior to performing study-specific duties.

15.3.3. Monitoring Reports

After each monitoring visit, the monitor will send to the Principal Investigator an e-mail or letter summarizing the monitoring visit. A monitoring report will be sent to the Sponsor. The report will include the date of the monitoring visit, the clinical site name, the name of the monitor, the name of the Investigator, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. The Principal Investigator will be responsible for ensuring that follow-up action items requiring resolution at the clinical site are completed in an accurate and timely manner.

15.3.4. Close-Out Visit

Final close-out visits at the clinical sites will be conducted at the end of the study. The purpose of the final visit is to collect all outstanding study data documents, ensure that the Principal Investigator's files are accurate and complete, review record retention requirements with the Principal Investigator, make a final accounting of all study supplies shipped to the Investigator/site, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

15.4. Data Management

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

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

Only authorized persons can complete eCRFs. eCRFs shall be signed by Investigators as specified on the delegation log included in the ISF.

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

15.4.1. Data Quality Assurance

ORACLE Clinical Remote Data Capture (OC/RDC) is the EDC system that will be deployed to support data collection for this study. Documentation pertinent to the use of the EDC system will be made available for use by appropriate clinical site personnel. All individuals who will be expected to use the EDC system will be given adequate training necessary to perform their assigned tasks as described in (21 CFR 11.10(i)). Training will be conducted by qualified individuals initially and on a continuing basis, as needed.

15.4.2. Data Handling

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

15.4.3. Data Ownership

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

15.5. Compliance

15.5.1. 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 this research clinical protocol, SOPs, applicable regulations and recognized standards and any additional requirements imposed by the IRB/REB or regulatory authority.

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

The Sponsor will secure an agreement with all parties to allow direct access to all study-related clinical sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor and/or its designee(s) and inspection by regulatory agencies.

The 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.

Data from eCRFs and other external data (i.e., core laboratory data) will be entered into a clinical database as specified in the data management plan.

The clinical database 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 clinical site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

15.5.2. Investigator Compliance

The Principal Investigator assumes full responsibility for performance of the research study in accordance with the Clinical Study Agreement, this clinical protocol, GCP, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IRB/REB. The Principal Investigator shall be responsible for the day-to-day conduct of the clinical investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

15.5.3. Onsite Audits

Representatives of the Sponsor may visit the clinical site(s) to 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 clinical study-related activities, independent of the employees involved in the clinical study.

Similar auditing 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 and/or institution shall permit the Sponsor and regulatory bodies (e.g., FDA) direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, IRB/REB review, and regulatory inspections.

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

15.6. Confidentiality

The Investigator and his/her study staff shall consider all information, results, discoveries; records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, records to any third party without the Sponsor's prior written consent.

IRB/REB members have the same obligation of 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.

15.7. Liability

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

15.8. CIP Amendments

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

The Sponsor will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the Investigators to obtain approval from their IRB/REB. The Investigator will only implement the amendment after approval of the IRB/REB and regulatory authority, unless the modifications increase subject safety. Administrative amendments to the Clinical Investigation Plan will be submitted to the regulatory authorities and IRB/REB for notification. Furthermore, Investigators shall sign any approved amendment for agreement. The clinical sites will receive the following for their regulatory file, and if applicable, IRB/REB submission:

- An updated clinical protocol
- Changes to ICF template (if necessary)

15.9. Record Retention

The Investigator shall maintain all study documentation in his/her possession and/or control and institute measures to prevent accidental or premature destruction of any data and/or documents related to the study.

The Investigator shall retain study documentation (the ISF, subject medical files and eCRFs) in accordance with local law and regulations during the study and for a minimum period of two (2) years (or longer if

local laws require) after the latter of the following two dates: The date on which the investigation is terminated or completed, or 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.

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

- The Sponsor shall retain the study documentation in accordance with local law and regulations during the study and for a minimum period of two (2) years (or longer if local laws require) after the latter of the following two dates: The date on which the investigation is terminated or completed, or 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.

15.10. Publication and Use of Information

The Sponsor intends to publish the results of this multi-center study. Individual Investigators are therefore asked to refrain from reporting results from their study participants prior to publication of the main multi-center report. 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 group 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 will enter the study into a public clinical trials repository such as ClinicalTrials.gov.

Participating subjects will not be identified by name in any published reports about the clinical study.

15.11. 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 clinical Investigators of the termination or suspension and the reason(s) for this. The Investigator shall then promptly inform the reviewing IRB/REB and provide the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled subjects will be asked to complete all remaining study visits and the subject will then be seen by the treating physician according to standard of care following intracranial aneurysm treatment.

The Sponsor, IRB/REB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing IRB/REB, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigation site is suspended or prematurely terminated, the Sponsor shall promptly inform the Investigator(s) of the termination or suspension and the reason(s). The Investigator shall then promptly inform the reviewing IRB/REB.

16. References

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17. Version History

Version	Summary of Changes	Author(s)/Title
Rev A	Not Applicable, New Document	Harsh Sancheti, Medical Writing Manager
Rev B	Changes to Schedule of Events based on FDA Feedback	Harsh Sancheti, Medical Writing Manager
Rev C	See table below "Changes in Rev C".	Maunil Desai, Medical Writer

Changes in Rev C

Sections Affected	Change in the Protocol	Rationale
Section 4.3, Section 5.1.1, Throughout the CIP	Addition of primary effectiveness endpoint to the study	Pipeline™ Vantage, a new generation Pipeline™ device, is being studied under IDE G170234. Thus, the study is being modified to be an effectiveness and safety study.
Section 13	Changes to sample size and statistical considerations	Addition of primary effectiveness endpoint to the study required changes to Statistical Design and Methods section.
Cover page, Section 14.2 and section 11.2	Addition of Local Sponsor – Canada and Health Canada specific requirements including ethics committee.	ADVANCE study will have centers in Canada and therefore Local Sponsor and ethics committee were updated to comply with Health Canada regulations.
Glossary and Table 9-1	mRS certified independent assessor	mRS certified independent assessor defined and certification requirements specified
Throughout the CIP	"Groin puncture" changed to "puncture at arterial access site"	CIP modified to ensure access to arterial vasculature is site-neutral
Throughout the CIP, specifically Section 7	Pipeline™ Shield device replaced with Pipeline™ Vantage device	Pipeline™ Vantage, a new generation Pipeline™ device, is being studied under IDE G170234.
Throughout the CIP	Any mention of "recanalization" with respect to the study changed to "recurrence"	Consistent and uniform usage of a single term "recurrence" to describe initial complete aneurysmal occlusion followed by incomplete occlusion at follow-up exam.

Section 4	Added additional information about clinical experience with Pipeline™ group of devices	Background section modified to provide additional data regarding the use of Pipeline™ group of devices
Section 6.2	Study rationale	Study rationale modified since Pipeline™ Vantage, a new generation Pipeline™ device, is being studied under IDE G170234.
Section 10.1	Potential Risks	Potential Risks revised as per comments by FDA.
Section 11.2	Reporting of adverse events	Adverse events can be reported electronically as well.
Section 12.2.4	Stenosis grading scale Changed to "CTA" from "MRA" imaging	Since there is a separate category for "no stenosis", 1st category of grading scale begins at 1-25%. Revision as per comments by FDA.
Section 9 (Table 9-1, Sections 9.2.4, 9.6, 9.9.2, 9.9.6)	Visit and Assessment Schedule table, 180-day imaging and follow-up visits	Defined the timepoint from which assessment of adverse events will begin and revisions as per comments by FDA.
Cover page	Sponsor changed from "Medtronic Neurovascular" to "Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic)"	Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic) manufactures the Pipeline™ Vantage device.
Section 15.6	Added text	Added language for compliance with data privacy laws.
Section 8.4	Exclusion criteria	In the exclusion criteria, one criterion was split into two for more clarity. As per comments by FDA, added exclusion criteria #20 and #33 and added clarifications to the exclusion criteria #13.
Section 9.9	1-year follow up	Clarification was added to ensure clinical follow up for subjects with failed device implant.

	2-year and 3-year follow up evaluations	Clarification was added regarding pregnancy test for 2-year and 3-year follow-up visits.
Section 15.1	Steering committee	Change made to align with Steering committee charter
Section 7.7 and 10.2	Requirement for Physicians	Clarified that physicians who are responsible for implanting the study device, Pipeline™ Vantage, need to self-attest to having completed a minimum of 20 cases with Pipeline™ Flex Embolization Device.
Section 9.5.1, Table 9-2	Ancillary devices' details	Added Table 9-2 that provides compatible microcatheter sizes for Pipeline™ Vantage. Also, added text regarding ancillary devices in general.
Section 12.2.1	Physician Screening Committee	Added that Physician Screening Committee will be responsible for determining subject eligibility in the study.
Section 15.2	Site selection requirement	Removed physician-specific requirement from the list of requirements for clinical sites.
Appendix Section 18.1	Center for Medicare and Medicaid Services (CMS) IDE Study Criteria added	Evidence provided regarding effect on Medicare beneficiaries

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.[261] Between 1996 and 2006, endovascular treatment of cerebral aneurysms increased from 20.1% to 67.0% per Medicare CPT codes.[261] In the PUFs study (**Section 4.2.2**) 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[262] 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 rate of Medicare beneficiaries undergoing coiling in cases of unruptured intracranial aneurysm increased almost 15-fold between 2000 and 2010.[263] Study results are expected to be generalizable within the Medicare beneficiary population based on the prevalence of unruptured intracranial aneurysm in patients age 65 and older.