Cover Page – Clinical Study Protocol

CLINICAL STUDY PROTOCOL	
Clinical Investigation Plan Title	Pipeline Flex with SHield Technology Embolization - An International MulticEnter ObservationaL Post Market StuDy of treated Intra Cranial Aneurysms (SHIELD)
Clinical Investigation Plan Identifier	NV-PED-010
CIP/Protocol number	Rev. B, 24 June 2016
ClinicalTrials.gov Identifier	NCT02719522

Medtronic

SHIELD

Pipeline Flex with SHield Technology Embolization- An International MulticEnter ObservationaL Post Market StuDy of treated Intra Cranial Aneurysms.

CLINICAL PROTOCOL

Protocol Number: NV-PED-010

REVISION: B, 24-Jun-2016

Sponsor:

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Signature: _____ Date: _____

[redacted] **/ Senior Clinical Quality Specialist APAC**

Signature: _____ Date: _____

[redacted] **/ Legal compliance ANZ**

Pipeline Shield Aneurysm Study: A Global Prospective Multicenter Observational Trial

Clinical Protocol Investigator Agreement

I will conduct the clinical study in accordance with this agreement, all requirements of the investigational plan, all applicable regulations, and any conditions of approval imposed by my reviewing Institutional Review Board (IRB) / Ethics Committee (EC), if applicable. I agree to abide by all of the responsibilities of Investigators and ICH Good Clinical Practice including but not limited to the following:

- If applicable, I will obtain written approval from the authorized IRB/EC for the institution at which this study will be conducted and I will submit the certification of IRB/EC approval and any conditions of this approval to the Sponsor.
- I will ensure that Informed Consent or Data Release Form (DRF) is obtained from each subject participating in this clinical study in accordance with the informed consent regulation, if applicable, and that a signed copy of the informed consent or DRF is available to the Sponsor and the Sponsor's designated monitor.
- I will ensure the timely reporting of adverse events to the Sponsor, the IRB/EC as required, and applicable regulatory agencies as required.
- I will ensure the accurate completion of protocol case report forms and, I will submit completed protocol case report forms, progress reports, and a final report as specified by the IRB/EC and/or regulations, if applicable.
- I will direct the retention of required records and documents related to the study according to regulatory and study protocol requirements.

_____	_____/_____/_____
Principal Investigator Signature	**DD MMM YYYY**
_____	_____/_____/_____
Sub-Investigator Signature	**DD MMM YYYY**
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Sub-Investigator Signature	**DD MMM YYYY**
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Sub-Investigator Signature	**DD MMM YYYY**

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Sponsor: Medtronic Neurovascular **9775 Toledo Way** **Irvine, California, USA 92618** **Telephone: 949.837.3700**	**Protocol Number:** NV-PED-10 **Product:** Pipeline™ Flex Embolization Device with Shield Technology™ **Regulatory Class:** III

Title: Pipeline Flex with SHield Technology Embolization- An International MulticEnter ObservationaL Post Market StuDy of treated Intra Cranial Aneurysms (SHIELD)

Study Design:

This is a prospective, single-arm, multi-center post-market observational study assessing the performance of the Pipeline™ Flex Embolization Device with Shield Technology™ in subjects undergoing treatment for intracranial aneurysms in a large real-world, post-market setting.

Objective:

To assess the performance of the Pipeline™ Flex Embolization Device with Shield Technology™ in subjects undergoing treatment for intracranial aneurysms in a large real-world, post-market setting.

Number of Subjects:	**Number of Study Centers:**
Up to 200 subjects	Up to 25 study centers

Duration of Study Participation:

- Enrollment Duration: Approximately 2 years
- Follow-up: 1 Year
- Total Study Duration: Approximately 3 years

Inclusion Criteria:

- Subject has provided written DRF or informed consent using the IRB/EC-approved consent form and agrees to comply with protocol requirements.
- At least 18 years of age.
- Subject has already been selected for flow diversion therapy as the appropriate treatment.
- Subject has a target IA that has a parent vessel with diameter 1.5-5.0 mm distal/proximal to the target IA.

PROTOCOL SYNOPSIS	
Sponsor: Medtronic Neurovascular **9775 Toledo Way** **Irvine, California, USA 92618** **Telephone: 949.837.3700**	**Protocol Number:** NV-PED-10 **Product:** Pipeline™ Flex Embolization Device with Shield Technology™ **Regulatory Class:** III

Exclusion Criteria:

1. Major surgery including endovascular procedures within the past 30 days.
2. Subject with target IA located in the basilar artery.
3. Subject with anatomy not appropriate for endovascular treatment due to severe intracranial vessel tortuosity or stenosis determined from baseline or pre-procedure imaging, or a history of intracranial vasospasm not responsive to medical therapy.
4. Stent is in place in the parent artery at the target IA location.
5. Subject with an acutely (within 30 days) ruptured aneurysm with a Hunt and Hess grade of 4 or higher.
6. Any known contraindication to treatment with the Pipeline™ Flex Embolization Device with Shield Technology™ per Instructions for Use.
7. 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, worsening of clinical condition in the last 30 days) may be compromised by the subject's enrollment.
8. Pregnant or breast-feeding women or women who wish to become pregnant during the length of study participation.
9. Subject is currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from Medtronic.
10. Legal incapacity or evidence that a subject cannot understand the purpose and risks of the study or inability to comply fully with study procedures.

Treatment/Follow-up:

Eligible subjects will be treated with the Pipeline™ Flex Embolization Device with Shield Technology™.

Subjects will undergo standard of care follow-up visits. Data generated per standard of care will be collected for 1 year beyond the index procedure. All follow-up visits and telephone calls during this time period will be recorded. A summary of the data to be collected is listed in the table below.

In order to track compliance with antiplatelet therapy, subjects will be contacted at a minimum of approximately 1 (±14 days), 3 (±30 days), 6 (±6 weeks), and 12 (±8 weeks) months post-index procedure and asked to confirm their current antiplatelet regimen and that all relevant adverse events have been reported.

A survey will be administered to all centers to collect their standard antiplatelet therapy regimen at the start of the study and annually.

Time Period	Data to be Collected
Baseline	• Relevant medical history and demographics • Aneurysm characteristics, symptoms and status (ruptured or unruptured) • Hunt & Hess Grade and WFNS (if ruptured) • Antiplatelet medication use within past 30 days • Other relevant concomitant medications • Platelet reactivity testing • NIH Stroke Scale (NIHSS) • Modified Rankin Scale (mRS)
Procedure	• Relevant medications including antiplatelet regimen • Adverse events • Platelet reactivity testing • Procedure and fluoroscopy times • Study device information including side branches covered • Concomitant treatments • Deployment success at target IA • Imaging to be sent to the Core Lab* • Aneurysm occlusion • NIHSS • mRS
Post-Implant Follow-up	• Relevant medications including antiplatelet regimen • Adverse events • Platelet reactivity testing • Imaging to be sent to the Core Lab* • Aneurysm occlusion • Retreatment • NIHSS • mRS

*All imaging taken (e.g., angiograms, CT, MR, rotational angiography with 3D reconstruction, cone-beam CT, etc.) should be provided to the Core Lab.

Statistical Analysis:

Descriptive statistics will be used to present the data and to summarize the study results. For continuous variables, statistics will include means, standard deviations, medians and ranges, as appropriate. Categorical variables will be summarized in frequency distributions. The unit of analysis for baseline demographics, study device usage and safety-related endpoints will be the subject. The unit of analysis for the device-related outcome will be the device. The unit of analysis for occlusion will be the aneurysm.

REVISION HISTORY

Revision	Effective Date	Change summary
Revision A	October 07, 2015	Initial Version
Revision B	June 24, 2016	• Australian requirements previously included in the addendum to Rev.A have been included in Rev.B. In particular: - List of device models has been added in section 2.1.1 - The sentence *"No other device or concomitant medications different from clinical practice have to be used during the SHIELD Study, since this is a post-market non-interventional study."* has been added in section 5.4 - The sentence *"Each investigator is to follow any individual local Competent Authority, Ethics Committee, IRB and TGA safety reporting requirements."* has been added in section 6.2 - The sentences *"It is the responsibility of the investigator and the clinical study teams to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse."* and *"All Regional Reporting requirements shall be followed: details will be specified in the Safety Management Plan."* have been added in section 7. - The sentence *"The regional Sponsor Medtronic Australasia is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB."* has been added in section 13.1 - The sentence *"For Australia, the Investigator shall retain and preserve a copy of all Study Materials, including copies of signed consent forms, Case Report Forms, Clinical Investigation Plan, information relating to the Investigational Product, correspondence and investigator files for at least 15 years from Study Completion and must ensure that no Study related materials are destroyed before the expiration of this time period without the written approval of Sponsor. The Institution agrees to notify the Sponsor before destroying any Study Materials and agrees to retain the Study Materials for such longer period as reasonably required by the Sponsor at the Sponsor's expense."* has been added in section 14.2 - Appendix A – Investigators list & Study Staff has been added

		• The development phase has been removed from the synopsis; • The number of patients has been changed in 200 (protocol synopsis and sections 4.1 and 4.2); • The number of sites has been changed in up to 25 (protocol synopsis and section 4.2); • The enrollment duration and the total study duration have been changed in approximately 2 years and approximately 3 years respectively (protocol synopsis and section 4.1); • Suggested FU windows have been added in the protocol synopsis and in sections 5.5 • The maximum number of patient enrolled for site has been changed in 30 in section 4.2; • Visit windows have been removed from sections 3.1 and 9.4; • The first sentence in section 5.12 has been changed from "*The Sponsor may choose to discontinue the study should the Sponsor discover additional information during the study that may cause harm to subject safety.*" to *"The Sponsor may choose to discontinue the study if the Sponsor discovers additional information during the study that may cause harm to subject or negatively affect subject safety."* • The adverse events causality assessment has been changed following the new regulations in section 6.1; • The list of adverse events that can be adjudicate by the CEC in section 8.1 has been removed since all events of interest will be adjudicate; • The characterization of major strokes has been added in section 9.4; • EC and IRB have been added as authorities that can request to have access to patient medical files in section 11.1; • Previous section 11.2 "Monitoring report" has been removed; • Experience Statement from Principal Investigators and Sub-Investigators has been added in section 17.4; • The possibility to conduct ORACLE training also through a website has been added in section 17.5; • The definition of stroke has been modified in section 21 while the following definitions have been added: Neurological Death, Transient Ischemic Attack (TIA), cerebral infarction, Intra-Cranial Hemorrhage (ICH).

1 INTRODUCTION

1.1 Purpose

The primary study objective is to assess the performance of the Pipeline™ Flex Embolization Device with Shield Technology™ in a large real-world, post-market setting.

1.2 Background and Significance

1.2.1 Clinical Background

Intracranial aneurysms (IAs) are common cerebrovascular abnormalities with a prevalence of 0.5-6% in adults.[1-4] Most IAs are asymptomatic until they rupture, which can occur suddenly and without warning. Rupture of an IA may lead to cerebral bleeding or subarachnoid hemorrhage (SAH), a devastating complication with a case-fatality rate of 51%.[5,6] Nearly half of SAH survivors are functionally incapacitated, with less than 5% having good outcomes.[5,6] Aneurysm size influences the likelihood of rupture and correlates with morbidity and mortality. Compared to smaller aneurysms, large aneurysms have a 3-fold higher probability of rupture within 5 years of diagnosis while giant aneurysms have a 9-fold higher probability of rupture within 1-2 years.[7,8] The ultimate goal of treatment of an unruptured aneurysm is to prevent rupture, while treatment of a ruptured aneurysm aims to prevent further hemorrhage.

1.2.2 Treatment

Despite advances in microsurgical techniques, treatment of large, giant, and wide-necked unruptured aneurysms with surgical clipping remains challenging and carries an associated mortality of 15-21% and morbidity of 9-35%.[9] Occlusion rates can be high for surgical clipping, however, many aneurysms are not amenable to open surgery and the procedure carries considerably higher overall risk.[10-12] The rates of morbidity and mortality for coiling range between 2.3-13% and 1.3-6.7%, respectively. [13-19] Coiling with balloons or stents has relatively low procedural risk, but these interventions have diminished efficacy for large, complex aneurysms, with occlusion rates as low as 40%.[20] Consequently, these low occlusion rates lead to high (27-50%) recurrence rates, may require retreatment, and ultimately place the patient at continuing risk for rupture. [20-25] Flow diverters such as the Pipeline™ Embolization Device (PED) have created a paradigm shift in the endovascular treatment of unruptured IAs, and their safety and efficacy have been demonstrated consistently.[26-36] Several studies evaluating the use of PED for treatment of unruptured small, large, and giant aneurysms have demonstrated achievement of high complete occlusion rates of 68-94.4% that are maintained up to 2-3 years after the index procedure with overall 0-13.9% associated morbidity/mortality rates. .[27,31,37] These rates compare very favorably to that reported in the literature with the use of conventional IA treatments of surgical clipping or coiling.[25,38]

1.2.3 Clinical Study Experience

The clinical benefits achieved with the use of use of Pipeline™ Embolization Device have been consistently demonstrated in multiple clinical trials.[26-36] 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).[27,30,37,39-41] Clinical outcomes from 5 key studies sponsored by Medtronic/Covidien have been summarized below:

Pipeline for Intracranial treatment of Aneurysms (PITA)

The PITA study was the first prospective multicenter trial of a flow-diverting construct for the treatment of complex large and giant IAs.[27] Thirty-one subjects with wide-necked (>4 mm) and unfavorable dome/neck ratios (<1.5 mm) and subjects with an IA 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 periprocedural stroke and no deaths occurred.

Pipeline™ Embolization Device for Uncoilable or Failed Aneurysms (PUFs)

The PUFs study was a multicenter, prospective, single-arm trial to evaluate the safety and effectiveness of the PED in complex large and giant IAs.[28] 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. 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, the rate of major ipsilateral stroke or neurologic death remained 5.6%.

International Retrospective Study of the Pipeline Embolization Device (IntrePED)

The IntrePED study was a retrospective global post market study of subjects treated with the PED at 17 centers worldwide.[29] 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 treated ruptured aneurysms was higher at 18.4% (14/76). Data from the IntrePED study report the safety of the PED in the treatment of various IAs in a real-world clinical setting.

Aneurysm Study of Pipeline in an Observational Registry (ASPIRe)

ASPIRe was a prospective, multi-center, single arm, post-market registry of 191 IA 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 14.5mm.

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% (13/191), 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 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 use of embolic coils was the most common adjunctive therapy and was employed in 17.3% (33/191) of subjects.

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 IAs in routine clinical practice, reporting a 6.8% rate of associated major morbidity and neurological mortality.

1.3 Rationale of the Clinical Study

The Pipeline™ Embolization Device demonstrates high efficacy and a good safety profile in treating aneurysms of diverse morphology. Continued development of the PED delivery system resulted in the Pipeline™ Flex Embolization Device (PFED), which incorporates a resheathing mechanism, allowing the physicians to reposition and redeploy the PED braid. Additionally, polytetrafluoroethylene (PTFE) sleeves are used in place of the protective coil, resulting in the elimination of the need to torque the delivery system to release the PED braid. The latest developmental modification to the PED system is Shield Technology™. Shield Technology™ utilizes a phosphorylcholine (PC) surface treatment to the existing implant combined with the PFED delivery system. 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 PFED implant based on bench data with human platelets and plasma. The study described herein will evaluate the performance of the Pipeline™ Flex Embolization Device with Shield Technology™ in a broad real-world clinical setting.

Platelet inhibition with dual antiplatelet therapy (DAPT); consisting of aspirin and a thienopyridine, is necessary for the prevention of acute or subacute thrombosis and related complications after neurointerventional procedures.[42] DAPT has been associated with a reduction in thromboembolic events, but has also been implicated as a potential factor contributing to the rates of ischemic and hemorrhagic complications associated with PED placement.[42] Current DAPT protocols used in PED patients are developed based on studies in the field of cardiology and interventional radiology. In addition, there is no consensus on the optimal DAPT regimen, dose, and duration.[43] This study aims to collect data on platelet function testing, DAPT regimens, optimal dose, and post-PED DAPT duration to identify their association with thrombotic and hemorrhagic adverse events in the clinical setting and evaluate related clinical outcomes.

2 DEVICE DESCRIPTION

2.1 Intended Use of Device

The latest developmental modification to the Pipeline™ Flex Embolization Device (PFED) system is Shield Technology™. Shield Technology™ utilizes a phosphorylcholine (PC) surface treatment to the implant combined with the PFED delivery system. 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 bare metal PFED implant based on bench data with human platelets and plasma.

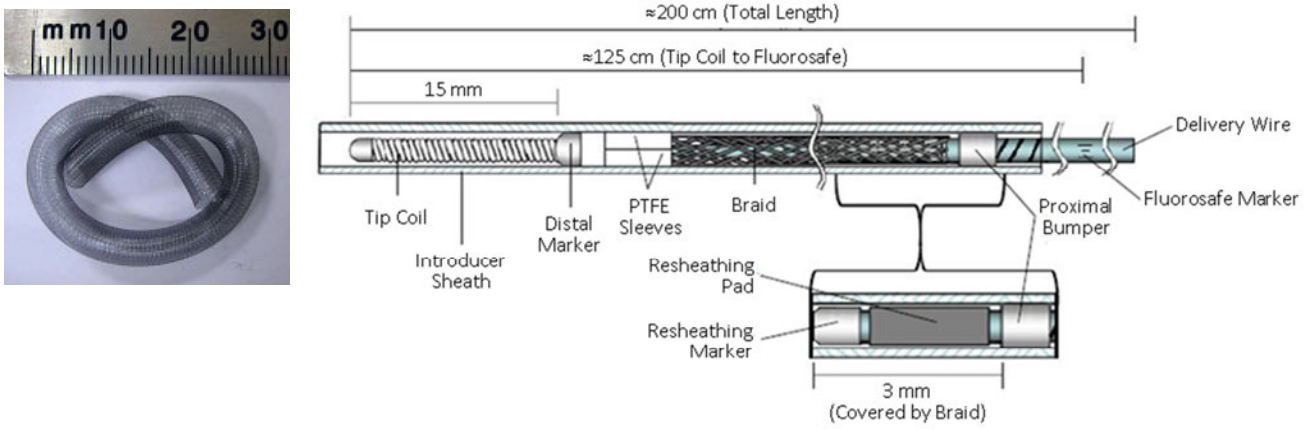
The Pipeline™ Flex Embolization Device with Shield Technology™ is intended for endovascular embolization of cerebral aneurysms and is designed to be placed across the opening (or 'neck') of a brain aneurysm and redirect blood flow away from the aneurysm, causing the blood within the aneurysm to clot. The device is designed for use in the neurovasculature.

2.1.1 Device Name

Name: Pipeline™ Flex Embolization Device with Shield Technology™.

A photo and diagram of the Pipeline™ Flex Embolization Device with Shield Technology™ is shown in Error! Reference source not found.**Figure 2.1**.

Figure 2-1. Pipeline™ Flex Embolization Device with Shield Technology™



Left, photo of the braid. Right, diagram of the distal end of the Pipeline™ Flex Embolization Device with Shield Technology™ delivery system loaded into the introducer sheath.

All the Pipeline™ Flex Embolization Device with Shield Technology™ models used in this trial are commercially available, CE-Marked and used within intended use in all the involved countries, including Australia. The table below reports all the available models' numbers:

MODEL NUMBER	Vessel (mm)	Length (mm)
PED2-250-10	2,50	10
PED2-250-12	2,50	12
PED2-250-14	2,50	14
PED2-250-16	2,50	16
PED2-250-18	2,50	18
PED2-250-20	2,50	20
PED2-275-10	2,75	10
PED2-275-12	2,75	12
PED2-275-14	2,75	14
PED2-275-16	2,75	16
PED2-275-18	2,75	18
PED2-275-20	2,75	20
PED2-300-10	3,00	10
PED2-300-12	3,00	12
PED2-300-14	3,00	14
PED2-300-16	3,00	16
PED2-300-18	3,00	18
PED2-300-20	3,00	20
PED2-300-25	3,00	25
PED2-300-30	3,00	30
PED2-300-35	3,00	35
PED2-325-10	3,25	10
PED2-325-12	3,25	12
PED2-325-14	3,25	14
PED2-325-16	3,25	16
PED2-325-18	3,25	18
PED2-325-20	3,25	20
PED2-325-25	3,25	25
PED2-325-30	3,25	30
PED2-325-35	3,25	35
PED2-350-10	3,50	10
PED2-350-12	3,50	12
PED2-350-14	3,50	14
PED2-350-16	3,50	16
PED2-350-18	3,50	18
PED2-350-20	3,50	20
PED2-350-25	3,50	25
PED2-350-30	3,50	30
PED2-350-35	3,50	35
PED2-375-10	3,75	10

PED2-375-12	3,75	12
PED2-375-14	3,75	14
PED2-375-16	3,75	16
PED2-375-18	3,75	18
PED2-375-20	3,75	20
PED2-375-25	3,75	25
PED2-375-30	3,75	30
PED2-375-35	3,75	35
PED2-400-10	4,00	10
PED2-400-12	4,00	12
PED2-400-14	4,00	14
PED2-400-16	4,00	16
PED2-400-18	4,00	18
PED2-400-20	4,00	20
PED2-400-25	4,00	25
PED2-400-30	4,00	30
PED2-400-35	4,00	35
PED2-425-10	4,25	10
PED2-425-12	4,25	12
PED2-425-14	4,25	14
PED2-425-16	4,25	16
PED2-425-18	4,25	18
PED2-425-20	4,25	20
PED2-425-25	4,25	25
PED2-425-30	4,25	30
PED2-425-35	4,25	35
PED2-450-10	4,50	10
PED2-450-12	4,50	12
PED2-450-14	4,50	14
PED2-450-16	4,50	16
PED2-450-18	4,50	18
PED2-450-20	4,50	20
PED2-450-25	4,50	25
PED2-450-30	4,50	30
PED2-450-35	4,50	35
PED2-475-10	4,75	10
PED2-475-12	4,75	12
PED2-475-14	4,75	14
PED2-475-16	4,75	16
PED2-475-18	4,75	18
PED2-475-20	4,75	20
PED2-475-25	4,75	25
PED2-475-30	4,75	30

PED2-475-35	4,75	35
PED2-500-10	5,00	10
PED2-500-12	5,00	12
PED2-500-14	5,00	14
PED2-500-16	5,00	16
PED2-500-18	5,00	18
PED2-500-20	5,00	20
PED2-500-25	5,00	25
PED2-500-30	5,00	30
PED2-500-35	5,00	35

2.2 Indication for Use

The Pipeline™ Flex embolization device with Shield Technology™ is intended for endovascular embolization of cerebral aneurysms.

2.3 Contraindications

- Patients who have not received antiplatelet agents prior to the procedure.
- Patients with active bacterial infection.
- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- The Pipeline™ Flex embolization device with Shield Technology™ should not be used alone as sole therapy for acutely ruptured aneurysms.

2.4 Device Labeling

The Pipeline™ Flex Embolization Device with Shield Technology™ is approved for commercialization in the countries that will be participating in this study and will be used within its intended use as specified in the approved labeling. The Pipeline™ Flex Embolization Device with Shield Technology™ will be labeled as commercially available and in accordance with applicable language requirements.

2.5 Device Tracking

The Pipeline™ Flex Embolization Device with Shield Technology™ is traced by lot number. The lot number of each Pipeline™ Flex Embolization Device with Shield Technology™ used in this study will be captured on the case report forms. Due to commercial availability, shipments will not be tracked for the study.

2.6 Pre-Clinical Testing

Biocompatibility Summary

All biocompatibility tests for The Pipeline™ Flex Embolization Device with Shield Technology™ were completed, and all test results passed the acceptance criteria (per ISO 10993-1:2009 and FDA G95-1).

[redacted] **Study Summary**

[redacted]

Overall Study Conclusion

[redacted]

[redacted] **Study Summary**

[redacted]

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

3 STUDY OBJECTIVE

The study objective is to assess the performance of the Pipeline™ Flex Embolization Device with Shield Technology™ in a large real-world, post-market setting.

3.1 Data Analyses

The following data will be analyzed in this study:

- Antiplatelet therapy regimen
- Adverse events related to antiplatelet therapy
- Platelet reactivity testing results
- Moderate and Severe bleeding events utilizing GUSTO criteria
- All intracranial hemorrhages and delayed intracranial hemorrhages (>30 days post-procedure)

- Index procedure time
- Number of Pipeline™ Flex Embolization Device with Shield Technology™ utilized
- Device deployment success rate at target site
- Aneurysm occlusion at 6 months, 1 year and at last follow-up
- Recurrence and retreatment rates at 1 year post-procedure and at last follow-up
- The composite percentage of patients with modified Rankin Scale of 0-2 or no change from baseline at 1 year and at last follow-up.
- Occurrence of major stroke in the territory supplied by the treated artery or neurological death. Stroke events will be further characterized based on whether:
  - Event was caused by thromboembolic events
  - Event was caused by side-branch occlusion due to the study device

For the purposes of this study protocol, stroke is defined as a focal neurological deficit of presumed vascular origin persisting more than 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 of symptom onset.

The definition includes:

- Subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, 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 by the investigator as major or minor:

- Major Stroke: A stroke, which is present after seven days and increases the NIH Stroke Scale of the subject by ≥ 4.
- Minor Stroke: A stroke, which resolves completely within seven days OR increases the NIH Stroke Scale of the subject by ≤ 3.

Neurological death is any subject death due to an underlying neurologic cause.

The safety events noted for analysis will be adjudicated by an independent clinical events committee (CEC) (**Section 8.1**). Aneurysm occlusion and recurrence will be evaluated by an independent core laboratory (**Section 8.2**).

4 STUDY DESIGN

This is a prospective, single-arm, multi-center post-market observational study to assess the performance of the Pipeline™ Flex Embolization Device with Shield Technology™ in subjects undergoing treatment for intracranial aneurysms.

4.1 Expected Duration of the Study and Subject Participation.

Up to 200 subjects who meet the Inclusion/Exclusion Criteria may be enrolled over a period of approximately 2 years to reach a target number of subjects. Study participation includes initial screening and baseline evaluation, treatment using the Pipeline™ Flex Embolization Device with Shield Technology™, and follow-up visits at the discretion of the treating physician for 1 year beyond the index procedure. The total study duration is expected to be approximately 3 years.

4.2 Number of Sites and Subjects

Up to 200 subjects at up to 25 sites worldwide may participate. Each participating investigational site should attempt to enroll at least 1 subject and will be allowed to enroll up to 30 subjects who meet all study eligibility criteria.

4.3 Study Population

The study population will consist of subjects who have an intracranial aneurysm and are enrolled in the study. The treated aneurysm may be ruptured (with a Hunt and Hess grade of ≤3) provided that the Pipeline™ Flex Embolization Device with Shield Technology™ is used according to its Instructions for Use and its intended use during the treatment regimen.

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 device or two overlapped devices, the multiple aneurysms treated by that device(s) may all be included in the study. A maximum of two overlapped devices in consecutive arterial segments will be permitted. The largest aneurysm meeting criteria will be designated the target aneurysm. For equal sized aneurysms, the Core Lab will designate the target aneurysm.
- If the subject has more than one aneurysm and all aneurysms requiring treatment cannot be covered by a single Pipeline device or two overlapped devices, the non-target aneurysms should be treated first. After waiting at least 30 days per exclusion criterion #1 below, the subject may return for Pipeline treatment of the target aneurysm.

4.3.1 Inclusion Criteria

Subjects must meet all of the following general inclusion criteria:

1. Subject has provided written DRF or informed consent using the IRB/EC-approved consent form and agrees to comply with protocol requirements.
2. At least 18 years of age.
3. Subject has already been selected for flow diversion therapy as the appropriate treatment.

4. Subject has a target IA that has a parent vessel with diameter 1.5-5.0 mm distal/proximal to the target IA.

4.3.2 Exclusion Criteria

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

1. Major surgery including endovascular procedures within the past 30 days.
2. Subject with target IA located in the basilar artery.
3. Subject with anatomy not appropriate for endovascular treatment due to severe intracranial vessel tortuosity or stenosis determined from baseline or pre-procedure imaging, or a history of intracranial vasospasm not responsive to medical therapy.
4. Stent is in place in the parent artery at the target IA location.
5. Subject with an acutely (within 30 days) ruptured aneurysm with a Hunt and Hess grade of 4 or higher.
6. Any known contraindication to treatment with the Pipeline™ Flex Embolization Device with Shield Technology™ per Instructions for Use.
7. 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, worsening of clinical condition in the last 30 days) may be compromised by the subject's enrollment.
8. Pregnant or breast-feeding women or women who wish to become pregnant during the length of study participation.
9. Subject is currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from Medtronic.
10. Legal incapacity or evidence that a subject cannot understand the purpose and risks of the study or inability to comply fully with study procedures.

4.3.3 Point of Enrollment

Given that the prospective study population consists of patients who are already selected for flow diversion therapy and that the screening assessments consist of standard patient diagnostics for this therapy, subjects are considered enrolled in the study once the subject has signed and dated the Informed Consent or DRF and the Pipeline™ Flex Embolization Device with Shield Technology™ is advanced into the micro catheter inside the subject.

5 STUDY PROCEDURES

5.1 Patient information process

Patient informed consent will be obtained in accordance with local laws and regulations. Whether to use an Informed Consent or Data Release Form (DRF) is dependent on local regulatory requirements and local EC/IRB requirements, if applicable. The strictest requirement will be applied. The Informed Consent or DRF must be approved by the sponsor and the Site's EC/IRB, if applicable.

Legally incompetent or unconscious subjects are not expected to be included in this study.

5.2 Informed Consent process

A thorough explanation will be provided to the subject (or legally authorized representative) as to the nature and objectives of this study. Details of the study should include (but are not limited to) the following terms:

- Purpose of the study
- Participation is voluntary, and there is no penalty for withdrawal
- Potential risks/benefits for participation
- Contact information to ask questions or voice concerns

The study investigator and/or staff are responsible for obtaining written informed consent from each potential subject. Informed consent should be obtained in written format and using a form approved by the local IRB/EC, if applicable. The form should contain standard language consistent with local policies for ensuring privacy of confidential information. All subjects must sign the informed consent prior to any procedures/tests that go beyond initial assessments associated with the standard care for subjects with intracranial aneurysms and before any study related treatment assessments are administered and subject-related health information can be entered into the study database.

It is the responsibility of the investigator to give each subject (or subject's legally authorized representative) prior to inclusion in the study, full and adequate verbal and written information regarding the objective of this study and the confidentiality of the data collected.

The Sponsor will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner. The Sponsor will revise the written Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC/IRB, if applicable, and a copy of this information must be provided to the participating subjects.

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

5.3 Data Release Form process

The investigator must obtain written DRF prior to releasing personal information of the subject.

During the consent discussion the investigator or his/her designee must fully inform the subject of the study in non-technical wording understandable for the subject.
The subject must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.
When the subject decides to participate in the clinical study, the written DRF must be signed and personally dated by the subject and the investigator.
After all persons have signed and dated the DRF the investigator must provide the subject with a copy of the signed and dated DRF.

5.4 Procedure

The Pipeline™ Flex Embolization Device with Shield Technology™ placement procedure is described in detail in the Instructions for Use (IFU) document. The investigator should review and understand the complete IFU prior to performing any Pipeline™ Flex Embolization Device with Shield Technology™ placement in this clinical study.

Recommendations: In addition to the Pipeline™ Flex Embolization Device with Shield Technology™ (study device), the following devices and equipment are recommended during the study procedure.

- A tri-axial system
- 0.027 microcatheter
- Navien support catheter
- Long sheath (minimum of 90 cm)

No other devices or concomitant medications different from clinical practice have to be used during the SHIELD Study, since this is a post-market non-interventional study.

5.5 Data Collection

Eligible subjects will be treated with the Pipeline™ Flex Embolization Device with Shield Technology™.

Subjects will undergo standard of care follow-up visits. Data generated per standard of care will be collected for 1 year (±8 weeks) beyond the index procedure. All follow-up visits and telephone calls during this time period will be recorded. A summary of the data to be collected is listed in **Table 5-1**.

In order to track compliance with antiplatelet therapy, subjects will be contacted at a minimum of approximately (±14 days), 3 (±30 days), 6 (±6 weeks), and 12 (±8 weeks) months post-index procedure and asked to confirm their current antiplatelet regimen and that all relevant adverse events (**Section 6**) have been reported.

A survey will be administered to all centers to collect their standard antiplatelet therapy regimen at the start of the study and annually.

Table 5-1. Data Collection

Time Period	Data to be Collected
Baseline	• Relevant medical history and demographics • Aneurysm characteristics, symptoms and status (ruptured or unruptured) • Hunt & Hess Grade and WFNS (if ruptured) • Antiplatelet medication use within past 30 days • Other relevant concomitant medications • Platelet reactivity testing • NIH Stroke Scale (NIHSS) • Modified Rankin Scale (mRS)
Procedure	• Relevant medications including antiplatelet regimen • Adverse events • Platelet reactivity testing • Procedure and fluoroscopy times • Study device information including side branches covered • Concomitant treatments • Deployment success at target IA • Imaging to be sent to the Core Lab* • Aneurysm occlusion • NIHSS • mRS
Post-Implant Follow-up	• Relevant medications including antiplatelet regimen • Adverse events • Platelet reactivity testing • Imaging to be sent to the Core Lab* • Aneurysm occlusion • Retreatment • NIHSS • mRS

*All imaging taken (e.g., angiograms, CT, MR, rotational angiography with 3D reconstruction, cone-beam CT, etc.) should be provided to the Core Lab.

5.6 Screen Failure

Subject will be considered a screen failure if:

- The subject signs the informed consent or DRF but fails to meet study inclusion/exclusion criteria during the screening and baseline phase.
- The subject signs the informed consent or DRF, meets the study inclusion/exclusion criteria but an attempt to implant the Pipeline™ Flex Embolization Device with Shield Technology™ is not performed.

Subjects that undergo consent but are screen failures will be exited from the study and will not be required to undergo any additional follow-up. Only the reason for subject screen failure will be recorded.

5.7 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 IRB/EC's procedure for providing updated information to clinical study subjects, if applicable.

5.8 Study Exit

The subject will be seen by the treating physician according to standard care following intracranial aneurysm treatment. One year post-procedure, the subject will exit the study and be exempt from further data collection.

5.9 Termination of Subject Participation

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 (PI) or Sponsor for safety or administrative reasons.

5.9.1 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. Whenever possible, the site staff should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. If the 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 to ensure clear documentation of the subject's withdrawal.

5.9.2 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 should they continue in the study. If a subject is withdrawn from the study, the investigator will promptly inform the subject and Sponsor.

5.9.3 Lost to Follow-up

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

5.10 Deviations to the Investigation

A protocol deviation is defined as an event where the investigator or study personnel did not conduct the study according to the clinical protocol. Deviations shall be reported to the Sponsor regardless of whether medically justifiable actions are taken to protect the subject in an emergency.

Except for a change that is intended to eliminate an immediate hazard to a subject, the protocol will be followed as described. Subject specific deviations and non-subject specific deviations will be reported. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific IRB/EC's reporting policies and procedures, if applicable.

Sites with a high rate of protocol deviations will be closely evaluated and are expected to implement corrective actions to prevent further deviations. If a site demonstrates persistent deviations, as described above, the site may be terminated.

5.11 Discontinuation by IRB/EC

Where applicable, the IRB/EC may choose to discontinue the study at any center(s) for which they granted approval if:

- The research study is not conducted in accordance with the IRB/EC's requirements.
- The research study indicates unexpected serious harm to subjects.

5.12 Study Discontinuation by Sponsor

The Sponsor may choose to discontinue the study if the Sponsor discovers additional information during the study that may cause harm to subject or negatively affect subject safety.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all clinical investigators of the termination or suspension and the reason(s) for this. Where applicable, the IRB/EC will also be informed, either by the Sponsor or investigator if a local IRB/EC is utilized, promptly and provided with the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled subjects will be asked to complete all remaining study visits and the subject will then be seen by the treating physician according to standard care following intracranial aneurysm treatment.

6 ADVERSE EVENTS

The following Adverse events will be collected during the course of the study on the eCRFs.

- All Adverse Events (AE) with an underlying neurological cause (Neurological Adverse Events)
- All Device Related Adverse Effects
- All Procedure Related Adverse Events
- All Bleeding Events
- All Serious Adverse Events (SAEs)

Adverse event status will be evaluated throughout the study. These will include events occurring from the point of enrollment until a subject exits the study. If the subject is enrolled and the study procedure is attempted, but the Pipeline™ Flex Embolization Device with Shield Technology™ is not implanted for any reason, subjects will be followed to discharge and relevant safety events will be collected. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious and/or

unexpected event requiring notification to the Sponsor, and, where applicable, regulatory agency and IRB/EC, within the specified reporting timeframe. AEs will be categorized using the definitions in **Section 6.1**.

All study AEs, as well as the treatment and follow-up required, should be documented in the subject's medical records and in the eCRF. All study SAEs that occur during the 1 year follow-up period will be followed by the investigator until resolution or until 30 days after the occurrence of that event. A list of potential anticipated adverse events is provided in **Section 10.2**.

Bleeding events will be captured as Adverse Events by the sites and will be graded according to the GUSTO[44] bleeding criteria as seen in

Table 6-1 by the Clinical Events Committee.

Table 6-1. GUSTO Bleeding Criteria

GUSTO Bleeding Category	Definition
Severe or Life-Threatening	Intracerebral hemorrhage Substantial hemodynamic compromise requiring treatment
Moderate	Requiring blood transfusion but not resulting in hemodynamic compromise
Mild	Bleeding that does not meet the above criteria

6.1 Adverse Event Definitions

An *Adverse Event* (AE) is defined as 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.

An *Adverse Device Effect* (ADE) is defined as an 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™ Flex Embolization Device with Shield Technology™ used during the procedure (Day 0).

> 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.

A *Serious Adverse Event* (SAE) is defined as an adverse event that

a) Led to death,

b) Led to 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-subject or prolonged 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 serious adverse event.

A *Serious Adverse Device Effect* (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011 3.36)

An *Unanticipated Serious Adverse Device Effect* (USADE) is defined as 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)

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.

Severity:

- 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.

Causality Assessment:

The relationship between the use of the:

- Medical device (Medical device investigated in the Investigation) and
- The medical -surgical procedure (Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events.)

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

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

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

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

3. Possible:
   The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases

were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

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

5. Causal relationship:

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

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

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

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

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Investigators will make the maximum effort to define and categorize the event and avoid these situations. 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".

6.2 Event Reporting

The investigator is required to report all SAEs and any USADEs within 24 hours after first learning of the event to the Sponsor (

Table 6-2). The primary method of reporting SAEs to the sponsor will be through the eCRFs. If the database is unavailable the investigator may send the information to the SAE email or SAE Hotline. As soon as the database becomes available, the investigator must complete data entry. The investigator will send all available supporting documentation (blinded/de-identified as to the subjects' identity) to the SAE Hotline.

Table 6-2. Expedited Adverse Event Reporting Requirements

UADEs/USADEs	Investigator will notify Sponsor of all UADEs and USADEs within 24 hours of being aware of the event.
SAEs	Investigator will notify Sponsor of all SAEs within 24 hours of being aware of the event.
Sponsor SAE Hotline contact information:	**Fax: 001 763-591-3295** **Email: SHIELDSAEHotline@medtronic.com**

As additional information becomes available, copies of that source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports, imaging studies and subject summaries etc. are requested for a complete evaluation of the event.

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

USADEs have expedited reporting requirements and must be reported per regulatory requirements.

Each investigator is to follow any individual local Competent Authority, Ethics Committee, IRB and TGA safety reporting requirements.

7 DEVICE SPECIFIC EVENT

A device-specific event (DSE) is any complaint, malfunction or deficiency of the device.

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).

Malfunction is defined as failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or Clinical Investigational Plan (ISO 14155:2011 3.27).

Devices/products (including regulatory approved components used in combination with an investigational product) used in this study are market release and commercially available. Therefore, Post Market Surveillance is applicable.

Device complaints are not within the scope of this study and will be handled according to standard Sponsor procedures: all device specific events must be reported to the Sponsor, EC/IRB (if applicable) and local authorities as required by governing law. If a device malfunction results in an adverse event for the subject, this adverse event will be considered a reportable adverse event and must be reported as an Adverse Event (AE).

It is the responsibility of the investigator and the clinical study teams to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse.

All Regional Reporting requirements shall be followed: details will be specified in the Safety Management Plan.

8 STUDY COMMITTEES

To avoid and minimize bias, an independent Clinical Events Committee and Core Laboratory will be in place to adjudicate safety events and assess aneurysm occlusion.

8.1 Clinical Events Committee (CEC)

A CEC will be in place for the study using 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. This committee will be responsible for the review and adjudication of all adverse events reported in the study.

The CEC will adjudicate to specified events of interest definitions (where available), event term, event start date, event relatedness, event severity, and event outcomes.

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

8.2 Imaging Core Laboratory

An imaging protocol will be provided to the site. The imaging core laboratory will be responsible for the qualitative image analysis to determine aneurysm characteristics, side branch coverage by the Pipeline device, aneurysm occlusion, parent artery stenosis, and device migration.

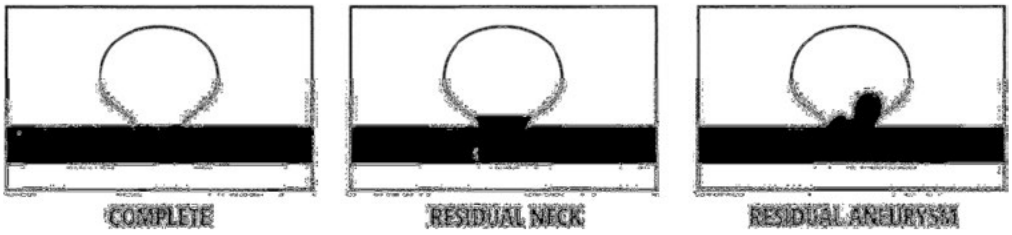
8.2.1 Baseline Anatomy

Imaging obtained immediately prior to the procedure will be reviewed to assess baseline aneurysm and parent artery characteristics.

8.2.2 Aneurysm Occlusion

Post-procedure angiograms will be reviewed to assess aneurysm occlusion according to the scale of Roy[5] (**Figure 8-1**).

Figure 8-1. Scale of Roy for Judging IA Endosaccular Embolization Success



- **Class 1 - Complete:** complete obliteration
- **Class 2 - Residual Neck:** the 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 sac

8.2.3 Parent Artery Stenosis

Post-procedure angiograms will be reviewed to assess stenosis in the parent artery and across the entire Pipeline™ device. Stenosis is calculated as the smallest measurable diameter of the Pipeline Device compared to the smallest measurable diameter of the proximal or distal normal parent artery. Stenosis will be measured and judged according to the scale in **Table 8-1**.

Table 8-1. Scoring System for Stenosis

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

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 General Principles

Descriptive statistics will be used to present the data and to summarize the results. For continuous variables, statistics will include means, standard deviations, medians and ranges, as appropriate. Categorical variables will be summarized in frequency distributions. In general, data for all study subjects combined will be presented. Individual data will be presented in subject

listings. Statistical analyses will be conducted in SAS version 9.1 or above (SAS Institute, Cary, NC) or other validated statistical software package.

For adverse event reporting, the primary analysis will be based on subject counts (e.g., the number and percentage of subjects with event among the total number of subjects). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of subjects with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x subjects.

For device-related outcomes (e.g., device deployment success rate), the unit of analysis will be device.

For occlusion outcomes, the unit of analysis will be the aneurysm.

9.2 Study Sample Size Assumptions and Justification

No formal statistical success criteria are proposed. Therefore, the sample size of the study is not based on statistical formulas for hypothesis testing of the primary outcome. Descriptive statistics will be provided for all analyses.

9.3 Analysis Population

The primary analysis sample will be based on the principle of intention-to-treat (ITT). All enrolled subjects who underwent the study procedure and in whom an attempt to implant the device was made will be included in the analysis population.

9.4 Analysis of Baseline Demographics and Procedural Characteristics

Descriptive statistics will be generated for pre-intervention demographics, aneurysm characteristics and procedural characteristics, device usage and adverse events. Categorical variables will be analyzed using frequency, incidence, and event rate. For continuous variables collected in the study, analysis will include mean, median, standard deviation, and range.

The following data points will be analyzed in this study:

- Antiplatelet therapy regimen
- Adverse events related to antiplatelet therapy
- Platelet reactivity testing results
- Moderate and Severe bleeding events utilizing GUSTO criteria
- All intracranial hemorrhages and delayed intracranial hemorrhages (>30 days post-procedure)
- Index procedure time
- Number of Pipeline™ Flex Embolization Device with Shield Technology™ utilized
- Device deployment success rate at target site
- Aneurysm occlusion at 6 months, 1 year and at last follow-up
- Recurrence and retreatment rates at 1 year post-procedure and at last follow-up

- The composite percentage of patients with modified Rankin Scale of 0-2 or no change from baseline at 1 year and at last follow-up.
- Occurrence of major stroke in the territory supplied by the treated artery or neurological death.

Major Stroke events will be further characterized based on whether:

- Event was caused by thromboembolic events
- Event was caused by side-branch occlusion due to the study device

9.5 Additional Analysis

All additional analyses are exploratory in nature. No formal statistical hypothesis will be proposed. Other additional analysis may be performed as requested by the investigators upon request.

9.6 Handling of Missing Data

All available data from enrolled subjects will be provided. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Adjustments for missing data will be performed if deemed necessary. Every effort will be made to ensure study follow-up visit compliance.

10 RISK/BENEFIT

10.1 Potential Benefits

Patients' participation in this study may offer no additional benefit in respect to the same treatments provided outside of the trial. However, the evidence collected in this study may help to improve future care.

The greatest clinical benefit of the Pipeline™ device includes restoration of original, natural blood circulation while providing permanent long-term IA occlusion. Intermediate benefits include stabilizing the aneurysm and providing symptomatic relief. The long-term complete occlusion rate of coil embolization in large or giant aneurysms appears to be far less than 50%, so flow diverters such as Pipeline™ Flex Embolization Device with Shield Technology™ would increase the likelihood that the procedure will provide full benefits to the subjects, without leaving behind coil mass which may cause significant symptoms following treatment.

10.2 Potential Risks

There are no expected additional risks relative to participation in this study as device used are commercially available and used in accordance with approved labeling. Therefore no risks other than the risks typically associated with routine device implantation and follow-up are anticipated. Patients are treated according to general clinical practice, therefore there are no additional risks associated with the participation in this study.

Potential risks associated with Pipeline™ Flex Embolization Device with Shield Technology™ use and diagnostic imaging for subjects with intracranial aneurysms undergoing an endovascular procedure include but are not limited to:

Risks associated with placement of the Pipeline™ Flex Embolization Device with Shield Technology™:

Possible	• Embolism • Headache • Hematoma • Hemorrhage, intracranial • Hemorrhage, non-intracranial • In-stent stenosis • Pain • Parent artery stenosis • Thromboembolic events • Vision impairment
Infrequent	• Amaurosis fugax (temporary loss of vision in one eye) • Aneurysm rupture • Arrhythmia • AV fistula • Blindness • Blood vessel perforation / rupture / occlusion • Carotid cavernous fistula • Cranial neuropathy • Death • Dizziness / tinnitus • Groin injury (including bleeding, bruising, infection, pain) • In-stent occlusion • Infection • Ischemia • Mass effect • Nausea / vomiting • Neurological deficits • Palsy / muscle weakness • Pseudoaneurysm • Ptosis • Stroke, hemorrhagic • Stroke, ischemic • Transient ischemic attack • Thrombosis / occlusion of the parent artery • Vasospasm
Rare	• Allergic reaction to medications and/or dye • Coma • Device fracture • Device migration or misplacement • Hydrocephalus • Seizure

Risks associated with imaging required for flow diverter treatment:

- Reddening of the skin, blistering and even ulceration
- Developing a radiation-induced cancer later in life
- Renal injury associated with contrast

Risks associated with Clinical Research

All records and other information about subjects participating in this study will be treated as confidential so there will not be additional risk for the patient's privacy that will be guaranteed.

Risk Mitigation

Several safeguards are incorporated into the study to minimize subject risk. All preclinical 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 will have completed at least 20 cases with a flow diverter of which at least 15 were with a Pipeline device including a minimum of 5 Pipeline™ Flex or Pipeline Flex with Shield Technology™ cases. All principal investigators have experience conducting clinical research and have adequate personnel to assure compliance to the study protocol. All clinical investigators will have received training specific to the Pipeline™ Flex Embolization Device with Shield Technology™. The Instructions for Use provide details on the proper use of the Pipeline™ Flex Embolization Device with Shield Technology™.

Subjects will be monitored closely as part of the study to allow for detection of adverse events, should they be present. Thus, in turn, should allow for early treatment, if necessary. Personally identifying subject information will not be collected on electronic Case Report Forms (eCRFs) or other study-related documentation to be provided to the Sponsor. In the event the Sponsor receives source documents or other information not yet redacted, the Sponsor will ensure confidentiality is maintained and appropriate de-identification is completed prior to filing in the study master file.

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. 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 Justification

The risks associated with use of the Pipeline™ Flex Embolization Device with Shield Technology™ are expected to be similar in nature and rate to those of the PED. Existing clinical studies and numerous independent publications with the PED provide clinical data to support the reasonable safety of the device. Therefore, the Sponsor considers the benefits of using the Pipeline™ Flex Embolization Device with Shield Technology™ to outweigh the risks in the defined subject population.

11 STUDY MONITORING

Medtronic, as the Sponsor, will be responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted in compliance with applicable regulations. Appropriately qualified and trained personnel appointed by Sponsor will conduct monitoring at each site per 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 Project Leader.

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Study Monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed investigator agreement, and compliance with IRB/EC 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 treatments, follow-up visits and phone conversations/interviews will be fully documented either in the subject's medical records or any other source documentation. Information entered into the eCRFs will be verified against the source documents and subject's medical records. Additional subject medical record review may be required for AE adjudication. De-identified study-related source documents may be photocopied, if required. The study Monitor will also check the Investigator Site File (ISF) to ensure that study-related documents are current.

A Medtronic representative or their agent may be present during the endovascular procedure.

11.1 Direct Access to Source 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/EC/IRB/regulatory agencies to have direct access to his/her research-related study records (e.g. medical records, source documentation, and billing information) for review. If an investigator is notified of a pending investigation by a regulatory agency, IRB/EC, or other similar organization, he/she will inform the Sponsor promptly.

11.2 Close-out Visit

Final close out visits at the sites will be conducted at the end of the study according to the Clinical Monitoring Plan. The purpose of the final visit is 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, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. Close-out visits may be conducted via telephone under appropriate conditions.

12 ELECTRONIC CASE REPORT FORMS (eCRFs)

Study data will be collected using electronic case report forms and a 21 CFR Part 11-compliant electronic data capture system. The application provides the capability of data collection remotely through the Internet so the participating site personnel may log on 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 review of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

The 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. All study staff that will enter data into eCRFs will undergo appropriate training for use of electronic CRFs.

Further information regarding eCRF navigation and use may be found in the eCRF Completion Guidelines.

13 RESEARCH COMPLIANCE

13.1 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 study protocol, Standard Operating Procedures, applicable regulations and recognized standards and, if applicable, any additional requirements imposed by the IRB/EC or regulatory authority.

The Sponsor is responsible for obtaining and maintaining appropriate insurance policies for the clinical study, if requested by the local regulations.

The regional Sponsor Medtronic Australasia is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and

custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB.

The Sponsor will secure an agreement with all parties to allow direct access to all study-related 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 will be entered into a clinical database as specified in the Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

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

During the course of the study, an amendment to the protocol may be necessary. Only the Sponsor is allowed to amend this protocol. Where applicable, any amendments or modifications must be approved by the research site's IRB/EC prior to research-study staff implementation, unless the modifications increase Subject safety. The research sites will receive the following for their regulatory file and, if applicable, IRB/EC submission:

- An updated protocol
- Changes to informed consent or DRF templates (if necessary)

13.2 Investigator Compliance

The site principal investigator assumes full responsibility for performance of the research study in accordance with the Clinical Study Agreement, this protocol, GCP, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IRB/EC.

13.3 Onsite Audits

Representatives of the Sponsor may visit the study site(s) to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy will be respected.

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

14 RESPONSIBILITIES AND RECORDS

14.1 Investigator Responsibilities

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.

14.2 Investigator 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 during the study and for a period of at least 2 years or longer, if required by local laws, after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

For Australia, the Investigator shall retain and preserve a copy of all Study Materials, including copies of signed consent forms, Case Report Forms, Clinical Investigation Plan, information relating to the Investigational Product, correspondence and investigator files for at least 15 years from Study Completion and must ensure that no Study related materials are destroyed before the expiration of this time period without the written approval of Sponsor. The Institution agrees to notify the Sponsor before destroying any Study Materials and agrees to retain the Study Materials for such longer period as reasonably required by the Sponsor at the Sponsor's expense.

14.3 Sponsor Record Retention

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

The Sponsor shall retain the study documentation during the study and for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

15 ETHICAL CONDUCT OF THE STUDY

This study is to be conducted in accordance with ethical principles based on the Declaration of Helsinki concerning medical research in humans and applicable regulations. This study is to be conducted in compliance with any additional laws and regulatory requirements of the country in which the site resides, including data protection laws.

The principles of the Declaration of Helsinki have all been implemented in this study by means of the informed consent/DRF process, EC/IRB approval (where applicable), study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

The investigator agrees by participating in the conduct of this protocol to adhere to the instructions and procedures described and to adhere to the principals of GCP.

16 INSTITUTIONAL REVIEW BOARDS / ETHICS COMMITTEE

The requirement to obtain EC/IRB approval depends on local law/hospital requirements.

If approval by the EC/IRB is required, the Sponsor and/or investigator must submit this protocol to the appropriate IRB/EC, and is required to forward to the Sponsor a copy of the written and dated approval.

The study (study number, protocol title, and version), documents reviewed (e.g. protocol, informed consent or DRF, etc.) and the date of the review should be clearly stated on the written IRB/EC approval/favorable opinion.

The study will not start at a site and subjects will not be enrolled until a copy of written and dated approval/favorable opinion has been received by the IRB/EC.

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

The informed consent or DRF used by the investigator for obtaining the subjects consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC for approval/favorable opinion.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Data Control

Every effort will be taken to ensure the accuracy and reliability of data including the selection of qualified investigators and appropriate study centers, review of 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. The Sponsor will review eCRFs for accuracy and completeness and any discrepancies will be resolved with the investigator or designee, as appropriate.

17.2 Site Selection

The Sponsor or representative of the Sponsor will assess each potential site to ensure the principal investigator and his/her staff has the facilities and expertise required for the study. Sites will be selected based upon a 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 study protocol.

To participate, a site must have the following components:

- A physician trained in the use of the Pipeline™ device with a history of completing at least 20 flow diversion cases of which a minimum of 15 are with a Pipeline device including a minimum of 5 Pipeline™ Flex or Pipeline Flex with Shield Technology™ cases.
- An established antiplatelet regimen used in conjunction with Pipeline™ device utilization.
- Commitment from the participating physician to pursue details of any safety outcomes.
- Commitment from the participating physician to enroll only subjects meeting the study criteria.
- Be willing to enter data and respond to queries.
- Internet access (for electronic data capture) in the hospital or clinic setting.
- Be willing to perform necessary documentation (e.g., eCRF).
- Agree to sign and adhere to the Investigator Agreement
- Agree to participate in Investigator meetings as scheduled by Medtronic.

17.3 Site Training

Each investigational site will be trained to the investigational plan. Investigator/Site Personnel will undergo training prior to performing any study-related procedures. All training must be documented. Study training requirements will include the following topics:

- Protocol review
- Delegation of authority for study-related tasks
- Informed Consent process, including any relevant IRB/EC requirements
- Electronic Case Report Forms and completion instructions
- Documentation of protocol deviations
- Adverse Event Reporting
- Device specific events reporting
- Instructions for Use of the Pipeline™ Flex Embolization Device with Shield Technology™
- Responsibilities and obligations of the investigator/staff
- General guidelines for good clinical practices
- Study documentation required (essential documents)

Existing study site personnel who have been delegated new tasks and new study site personnel will undergo training to the investigational plan, as appropriate.

17.4 Site Initiation

The Sponsor or a representative of the Sponsor will conduct a training session with site staff to review the protocol, eCRFs, the informed consent or DRF process, IRB/EC involvement (if applicable) and guidelines, responsibilities and obligations, reporting requirements, and general guidelines for good clinical practices.

Prior to enrolling subjects at an investigational site, the following documentation must be provided to the Sponsor:

- IRB/EC approval for the Investigational Plan, if applicable
- IRB/EC and Sponsor approved Informed Consent or DRF for the study, if applicable
- Signed Confidentiality Agreement (CDA)
- Signed Clinical Study Agreement (CSA), Investigator Agreement and if applicable, Sub-Investigator Agreement(s)
- Training log documentation to verify the appropriate study staff has been trained on the protocol, eCRFs, and study conduct.
- Investigator(s') *curriculum vitae* (CV)
- Experience Statement from Principal Investigators and Sub-Investigators

17.5 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 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 through a website or by qualified individuals initially and on a continuing basis, as needed.

17.6 Data Handling

The Sponsor is responsible for compilation and verification of the study data, retention of the clinical study database, performance of statistical analysis, 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.

18 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.

19 CONFIDENTIALITY

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

Where applicable, IRB/EC members have the same obligation of confidentiality.

20 PUBLICATIONS

The Sponsor intends to publish the results of this multicenter study. Individual investigators are therefore asked to refrain from reporting results from their study participants prior to publication of the main multicenter report. The Sponsor will establish authorship criteria for such 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.

21 DEFINITIONS

TERM	DEFINITION
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.
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.
Device Migration	Movement of one or more Pipeline™ Flex Embolization Device with Shield Technology™ of more than 5 mm in its parent artery location in comparison to the post-placement angiogram.
Device-related Adverse Effect	Event has a strong temporal relationship to the study device, and alternative etiology is less likely.

TERM	DEFINITION
Procedure	The primary study procedure involving the placement of the Pipeline™ Flex Embolization Device with Shield Technology™ at Day 0.
Neurological Adverse Event	An adverse event with an underlying neurological cause.
Neurological Death	Subject death due to neurologic reasons.
Point of Enrollment	Once the subject has signed and dated the Informed Consent or DRF, point at which the Pipeline™ Flex Embolization Device with Shield Technology™ is advanced into the micro catheter inside the subject.
Procedure-related Adverse Event	Event has a strong temporal relationship to the procedure (Day 0). This includes AEs attributable to any device(s) other than the Pipeline™ device used at procedure (Day 0), such as access devices, delivery microcatheters, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for treatment of intracranial aneurysms.
Retreatment	Any subsequent intervention (post study procedure with Pipeline implant) performed to treat the target IA.
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 a. A life-threatening illness or injury, or b. A permanent impairment of a body structure or a body function, or c. In-subject or prolonged 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 serious adverse event.
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)

TERM	DEFINITION
Stroke	A focal neurological deficit of presumed vascular origin persisting more than 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 of symptom onset. The definition includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. The definition also includes 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. The definition also excludes stroke events in cases of blood disorders such as leukemia or external events such as trauma. Stroke severity will be graded by the CEC as major or minor: Major Stroke: A stroke, which is present after seven days and increases the NIH Stroke Scale of the subject by ≥ 4. Minor Stroke: A stroke, which resolves completely within seven days OR increases the NIH Stroke Scale of the subject by ≤ 3. Each major stroke will further be categorized , with respect to : - Event was caused by thromboembolic events - Event was caused by side-branch occlusion due to the study device
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) 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.
Neurological Death	Any subject death due to neurological reasons.
Transient Ischemic Attack (TIA)	Transient Ischemic Attack is defined as neurological deficit symptoms lasting ≤24 hrs with no evidence of cerebral infarction on imaging.
Cerebral Infarction	Cerebral Infarction is defined as evidence of new ischemic changes (infarction) on imaging with no associated symptoms or symptoms lasting ≤24 hours.
Intra-Cranial Hemorrhage (ICH)	Intra-Cranial hemorrhage is defined as hemorrhage within the fixed vault of the cranium (skull). Intra-Cranial Hemorrhage will be further categorized by the CEC as: o **Intra Cerebral Hemorrhage (further categorized as):** ▪ ***Intra-Parenchymal Hemorrhage (IPH):*** Bleeding within the cerebral matter (brain parenchyma), not involving the ventricles. ▪ ***Intra Ventricular Hemorrhage (IVH)****: hemorrhage within the ventricles* o **Sub Arachnoid Hemorrhage (SAH):** Bleeding into the subarachnoid

TERM	DEFINITION
	space—the area between the arachnoid membrane and the pia mater surrounding the brain o **Subdural Hematoma (SDH):** Occurs when there is tearing of the bridging vein between the cerebral cortex and a draining venous sinus o **Epidural Hematoma (EDH):** A rapidly accumulating hematoma between the dura mater and the cranium

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Appendix A – Investigators list & Study Staff

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

A list of Study Contacts, including Name, title, address, and telephone number(s) of Sponsor SAE Hotline contact information, Sponsor Global Project Manager, Local Monitors and Sponsor Medical Expert will be maintained and regularly updated.