CLINICAL STUDY PROTOCOL

A PROSPECTIVE, MULTI-CENTER, SINGLE ARM STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF THE PULSERIDER® ANEURYSM NECK RECONSTRUCTION DEVICE USED IN CONJUNCTION WITH ENDOVASCULAR COIL EMBOLIZATION IN THE TREATMENT OF WIDE-NECK BIFURCATION INTRACRANIAL ANEURYSMS

NAPA STUDY

Protocol Number: CLIN-0034

Version: 3.0

November 13, 2017

History of Changes

Version Date	Description
Version 1.0— 23AUG2017	Original Document – not implemented
Version 2.0— 22SEP2017	Amendment per FDA Feedback
Version 3.0—13NOV2017	Amendment per FDA Study Considerations

Sponsor: Pulsar Vascular, Inc.
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Table of Contents

List of Figures and Tables

LIST OF ABBREVIATIONS

ACOM	Anterior Communicating Artery
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CT	Computed Tomography
CTA	Computed Tomography Angiography
DAPT	Dual Anti-Platelet Therapy
DMC	Data Monitoring Committee
DSA	Digital Subtraction Angiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDH	Epidural Hemorrhage
EVT	Endovascular Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDE	Humanitarian Device Exemption
HECON	Health Economics
HIPAA	Health Insurance Portability and Accountability Act
HUD	Humanitarian Use Device
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for Use
IPH	Intraparenchymal Hemorrhage
IRB	Institutional Review Board
ISAT	International Subarachnoid Aneurysm Trial
mITT	Modified Intent-to-Treat
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PG	Performance Goal
PHI	Protected Health Information
PP	Per Protocol
PI	Principal Investigator
RHV	Rotating Hemostasis Valves
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SC	Surgical Clipping
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDV	Source Data Verification
SDH	Subdural Hemorrhage
SOC	Standard of Care
SOP	Standard Operating Procedure
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
WBC	White Blood Cell
WNBA	Wide Neck Bifurcation Aneurysms

KEY ROLES AND RESPONSIBILITIES

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PROTOCOL AGREEMENT AND STATEMENT OF COMPLIANCE FORM

STUDY NAME AND NUMBER: NAPA - CLIN-0034 (CSC_2017_01)

STUDY TITLE: A Prospective, Multi-Center, Single Arm Study to Evaluate the Safety and Effectiveness of the PulseRider® Aneurysm Neck Reconstruction Device Used in Conjunction with Endovascular Coil Embolization in the Treatment of Wide-Neck Bifurcation Intracranial Aneurysms

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I have read this protocol and agree to conduct this clinical study in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practice (GCP), applicable FDA regulations (21 CFR Parts 812, 11, 50, 54 and 56), local regulations, the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB.

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB, the FDA, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor.

Principal Investigator (PI) Name (PRINT)	Signature	Date

PROTOCOL SUMMARY

Title of Study:	A Prospective, Multi-Center, Single Arm Study to Evaluate the Safety and Effectiveness of the PulseRider® Aneurysm Neck Reconstruction Device Used in Conjunction with Endovascular Coil Embolization in the Treatment of Wide-Neck Bifurcation Intracranial Aneurysms
Study Name	NAPA
Study Device:	PulseRider® Aneurysm Neck Reconstruction Device
Indication Under Investigation:	Indicated for use with neurovascular embolic coils in patients ≥ 18 years of age for the treatment of unruptured wide-neck intracranial aneurysms with neck widths ≥ 4 mm or dome to neck ratio < 2 originating on or near a vessel bifurcation of the basilar artery, middle cerebral artery, anterior communicating artery or carotid terminus with at least a portion of the aneurysm neck overlapping the lumen of the parent artery. The inflow vessels should have diameters from 2.0 mm to 4.5 mm.
Comparator Device:	This is a single arm study with no comparator device
Study Sponsor:	Pulsar Vascular, Inc. 130 Knowles Drive, Suite E Los Gatos, CA 95032 USA
Study Objectives:	The objective of this study is to evaluate the safety and effectiveness of the PulseRider® Aneurysm Neck Reconstruction Device in conjunction with coil embolization in the endovascular treatment of unruptured wide-neck intracranial aneurysms located at the bifurcation of the basilar artery, carotid terminus, middle cerebral artery (MCA), and anterior communicating artery (ACOM).
Study Design:	This is a prospective, multi-center, single arm, clinical study in which 160 subjects will be enrolled and followed at 30 days, 180 days, 1 year, 2 years, 3 years, 4 years and 5 years post-procedure.
Sample Size:	A total of 160 subjects will be enrolled into the study.
Number of Sites:	Up to 28 clinical sites in the US
Study Population:	Subjects with unruptured, angiographically confirmed wide-neck (≥ 4 mm or a dome-to-neck ratio < 2) intracranial aneurysms located at the bifurcation of the basilar artery, carotid terminus, MCA and ACOM arising from the parent vessel for the target aneurysm with a diameter of 2.0 mm to 4.5 mm will be eligible for the study.

Study Procedures:

The study evaluation time points include:

1. Screening/Baseline
2. Procedure
3. Hospital Discharge
4. 30 Day Follow-up (Clinic Visit)
5. 180 Day Follow-up (Clinic Visit)
6. 1 Year Follow-up (Clinic Visit and DSA)
7. 2 Year Follow-up (Telephone Call)
8. 3 Year Follow-up (Clinic Visit and DSA or MRA)
9. 4 Year Follow-up (Telephone Call)
10. 5 Year Follow-up (Clinic Visit and DSA or MRA)

Primary Safety Endpoint:

Composite of Neurological Death or Major Ipsilateral Stroke (in downstream territory) up to 1 year post-procedure:

- ***Stroke*** *is defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours with no apparent cause other than of vascular origin, including ischemic stroke and/or hemorrhagic stroke (i.e., intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EDH)). [Hatano 1976].*
- ***Major Stroke*** *is defined as stroke with symptoms persisting for more than 24 hours AND a sudden increase in the NIHSS of the subject by* $\geq$ *4.*

Primary Effectiveness Endpoint:

Complete Occlusion:
Rate of complete aneurysm occlusion (Raymond I) without significant parent artery stenosis (> 50% stenosis) or prior retreatment at 1 year post-procedure.

Secondary Effectiveness Endpoints:

- Technical Success is defined as successful implantation of device— physician able to access target aneurysm, deploy PulseRider® device at the neck of aneurysm and device was detached successfully
- Ability to retain embolic coils within aneurysm immediately post-procedure (as evaluated by the core lab)
- Complete aneurysm occlusion at 3 years and 5 years
- Adequate aneurysm occlusion (defined as Raymond I and II combined) at 1 year, 3 years and 5 years

- The percentage of target aneurysms that are retreated through 1 year, 3 years and 5 years
- The percentage of subjects with significant stenosis defined as > 50% at implant site at 1 year, 3 years and 5 years.
- The percentage of subjects with mRS 0-2 at 1 year, 3 years and 5 years

Additional Endpoints:

- The percentage of target aneurysm rupture up to 1 year, 3 years and 5 years
- No migration (defined as ≤ 2 mm) of the device at 1 year, 3 years and 5 years

Sample Size Justification

A meta-analysis was executed to determine the Performance Goal (PG) for the primary safety endpoint of a clinical study of the PulseRider®. Based on this meta-analysis, a rate of 9.9% rounded to 10% (95% CI: 5.9% - 16.1%) for death due to neurological causes or major ipsilateral stroke was calculated. A 5% margin of indifference for the primary safety endpoint is proposed, resulting in a PG of 15% for this endpoint. Based on the 1 year results of the ANSWER HDE Study, the anticipated rate for the primary safety endpoint is 7%. Results from a recently published meta-analysis [Fiorella 2017] indicate that the rate of complete occlusion at 1 year of wide-neck bifurcated aneurysms treated with conventional therapies is 46.3% (95% CI: 39.2% - 53.4%) whereas the ANSWER HDE Study described above reports the rate of complete occlusion is 58.8% with the PulseRider® device. With Sponsor's desire to seek strict superiority to a PG of 46.3% for the primary effectiveness endpoint and an expected attrition rate of 10%, one hundred sixty (160) subjects will provide 80% power for the primary safety endpoint and 85% power for the primary effectiveness endpoint.

Statistical Analysis

The primary safety endpoint will be evaluated on all subjects for whom implantation of the PulseRider® device was attempted. Subjects with a missing endpoint will be imputed with a multiple imputation method that will make use of the similarities between the subject's demographic, procedural, and aneurysm characteristics with those of the subjects with a non-missing endpoint. The endpoint will be considered successful if the upper bound of the two-sided 95% confidence interval for its rate is less than a performance goal of 15%.

The primary effectiveness endpoint will be evaluated on all subjects for whom implantation of the PulseRider® device was successful. Subjects with a missing endpoint will be imputed using a multiple imputation method that will make use of the subject's own past

occlusion evaluations and the similarities between the subject's demographic, procedural, and aneurysm characteristics with those of the subjects with a non-missing endpoint. The endpoint will be considered successful if the lower bound of the two-sided 95% normal approximation based confidence interval for its rate is greater than a performance goal of 46.3%.

The study will be deemed a success if the primary safety and effectiveness endpoints are met.

If the primary endpoints are met, the secondary effectiveness endpoint of technical success will be tested against a PG of 79%.

Inclusion Criteria

1. Subject with an angiographically confirmed digital subtraction angiogram (DSA) or computed tomography angiogram (CTA), of wide- neck (≥ 4 mm or dome to neck ratio < 2) intracranial aneurysm located at a bifurcation of the basilar artery, carotid terminus, MCA or ACOM

2. The parent vessel for the target aneurysm has a diameter of 2.0 mm to 4.5 mm

3. The subject is between 18 and 80 years of age the time of consent

4. Informed consent is obtained and the subject signs the Institutional Review Board (IRB) approved consent prior to beginning any study procedures along with the HIPAA Authorization for the release of PHI

5. In the opinion of the treating physician, placement of the PulseRider® device is technically feasible and clinically indicated

6. Subject has the mental capacity, willingness and ability to comply with protocol requirements and follow-up through 5 years for the clinical study

Exclusion Criteria

1. Unstable neurological deficit (condition worsening within the last 90 days)

2. Subarachnoid Hemorrhage within the last 60 days

3. Irreversible bleeding disorder

4. Modified Rankin Score (mRS) score ≥ 3

5. Patient has another intracranial aneurysm that in the Investigator's opinion, may require treatment within the 1 year follow up period

6. Patient has previously had two or more (≥ 2) procedures to treat the target aneurysm

7. Patient with an untreated target aneurysm that is partially thrombosed

8. Platelet count < 100 x 103 cells/mm^3

9. Inability to tolerate, adverse reaction to or any contraindication to taking aspirin or P2Y12 inhibitor

10. A history of contrast allergy that cannot be medically controlled

11. Known allergy to nickel

12. Relative contraindication to angiography (e.g. serum creatinine > 2.5 mg/dL)

13. Woman of child-bearing potential who cannot provide a negative pregnancy test

14. Evidence of active systemic infection (e.g. fever with temperature > 38°C/100.4°F and/or white blood cell (WBC) > 15,000)

15. Conditions that carry a high risk of neurological events or stroke (e.g., uncontrolled hypertension, prior ischemic stroke, Moya moya disease)

16. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 5 year follow-up period

17. Vessel tortuosity or stenosis that prohibits safe endovascular access to the target aneurysm to allow for treatment with the study device

18. Current involvement in a study for another investigational product

19. Patient and / or family considering a move from this geographical location at the time of consent

20. Categorized as a vulnerable population and require special treatment with respect to safeguards of well-being (e.g. cognitively impaired, veteran, prisoner, etc.)

Investigational Device: PulseRider® Aneurysm Neck Reconstruction Device

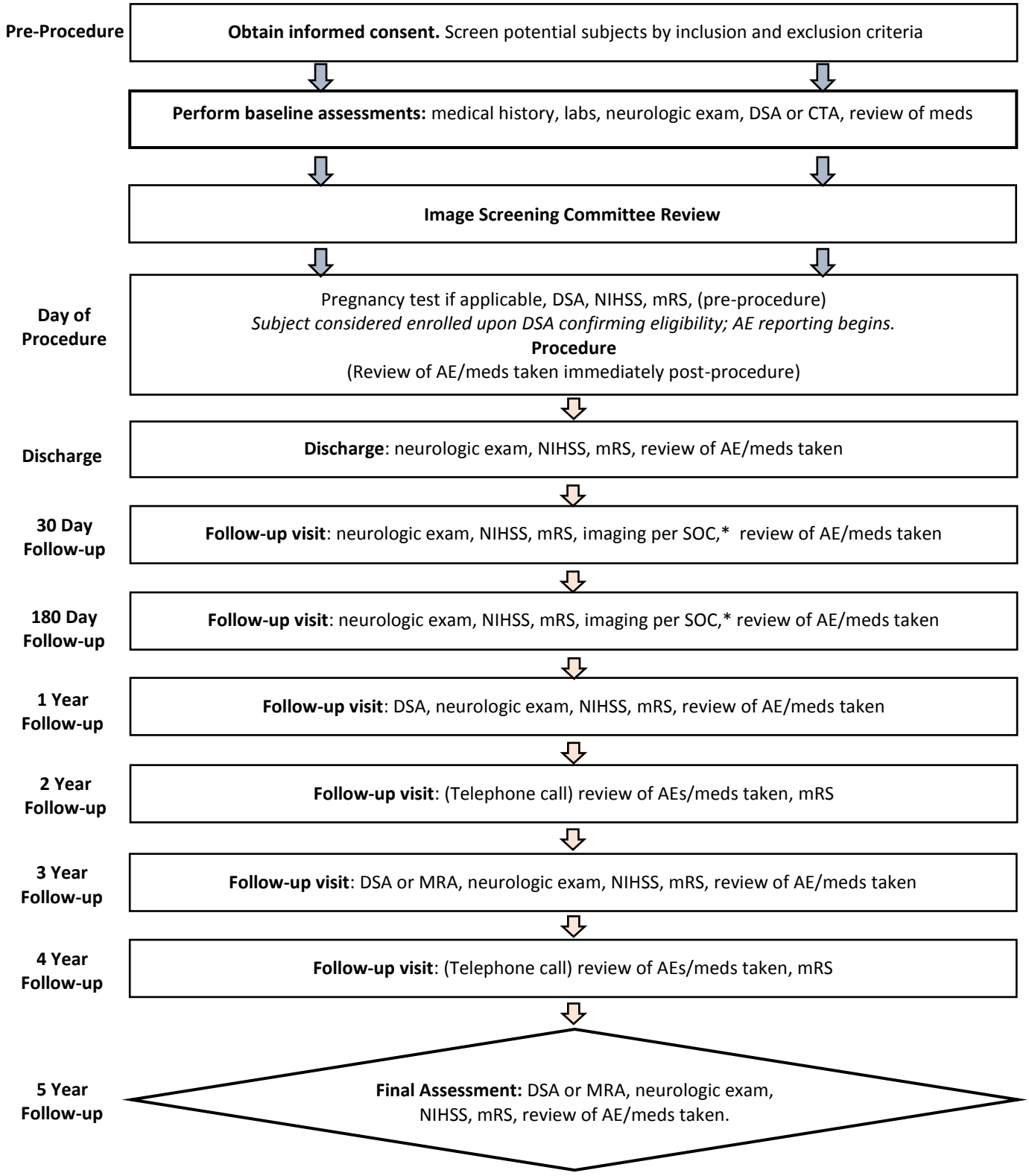
Study Duration:	The study duration is expected to be 6.5 years (including enrollment phase). The enrollment phase is expected to take 18 months following enrollment of the first subject.
Participant Duration:	It will take each participant approximately 5 years to complete the protocol required follow-up visits.

Schedule of Assessments

Assessments	Pre-procedure* (0-60 days of the procedure)	Immediately Pre-Procedure	Procedure	Immediately Post-procedure	Discharge	30 Day Follow-up (+/- 7 days)	180 Day Follow-up (+/- 42 days)	1 Year Follow-up (+/- 60 days)	2 Year Telephone Call (+/- 60 days)	3 Year Follow-up (+/- 60 days)	4 Year Telephone Call (+/- 60 days)	5 Year Follow-up (+/- 60 days)	Unscheduled Visit
Informed Consent	**X**												
Medical History	**X**												
Labs (CBC & Blood Coagulation Tests)	**X**												
Neurological Exam	**X**				**X**	**X**	**X**	**X**		**X**		**X**	**X**
NIH Stroke Scale Assessment		**X**			**X**	**X**	**X**	**X**		**X**		**X**	**X**
Modified Rankin Scale		**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Pregnancy Test		**X**‡											
Conventional Catheter Angiography – DSA	**X**	***X				**O**β	**O**β	**X**†$	**O**β	**X**††	**O**β	**X**††	
MR Angiography						**O**β	**O**β		**O**β	**X**††	**O**β	**X**††	**O**β
CT Angiography	**X**					**O**β	**O**β		**O**β		**O**β		**O**β
Review of Adverse Events			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Review of Medications Taken	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Medical Resource HECON		X	X	X	X	X	X	X	X	X	X	X	X

*With the exception of the baseline DSA or CTA and the pregnancy test, all baseline evaluations must be completed within 60 days prior to the index procedure and may occur on the procedure day prior to the procedure.
**Baseline imaging may be either CTA or DSA and must be completed within 180 days prior to the index procedure.
***Three treatment angiograms: 1) Immediately pre-procedure image is before PulseRider implant to confirm eligibility 2) Procedure image immediately after PulseRider placement 3) Immediately post-procedure is after coiling.
β Any imaging related to the target aneurysm conducted post-procedure and prior to the final study visit, per standard of care, will be collected.
† Imaging for 1 year post-procedure must be DSA.
†† Imaging for 3 and 5 years post-procedure must be DSA or Magnetic Resonance Angiography (MRA).
‡ Pregnancy test must be completed on day of procedure for women of childbearing potential.
$ Subjects who were not implanted with the PulseRider device are not required to undergo DSA imaging at 1 year.

SCHEMATIC OF STUDY DESIGN



*All imaging performed per standard of care (SOC) after the study procedure and prior to the final visit will be submitted to the core lab.

1. Background Information and Scientific Rationale

1.1. Background Information

An intracranial aneurysm is an abnormal dilatation that occurs in an artery as the result of a weakening in the wall of the vessel. This balloon like outpouching fills with blood and may enlarge over time; most commonly this occurs at the junctions or bifurcations of major arteries. As the aneurysm increases in size, the vessel wall becomes thinner and more fragile and is at risk of rupture. Many intracranial aneurysms remain silent and are never diagnosed unless they rupture resulting in a subarachnoid hemorrhage (SAH) or gradually enlarge over time and exert pressure on the surrounding brain tissue resulting in a variety of morbidities. These aneurysms are typically diagnosed because of the associated symptoms e.g. cranial neuropathies, visual disturbances, etc. Asymptomatic, unruptured aneurysms may also be discovered incidentally as a result of some other suspected pathology e.g. migraine headache, dizziness, etc. that requires diagnostic imagining. The most common presentation of an intracranial aneurysm however, is SAH, which is a life-threatening event. Even with prompt medical attention there is a high incidence of morbidity and mortality. Between 40% and 67% of ruptured aneurysms result in death within one month and 10% to 20% of the survivors have major morbidities [Woo 2002]. The primary goal of surgery or endovascular treatment of any aneurysm is to reduce the risk of initial or recurrent subarachnoid hemorrhage by excluding the lesion from the cerebral circulation.

Risk factors for the formation of aneurysms include a family history, various inherited disorders such as polycystic kidney disease, age greater than 50 years, female gender, hypertension, trauma, atherosclerosis, abnormal flow at a vessel bifurcation and current cigarette smoking [Vega 2002]. A strong female predilection has been observed in patients with aneurysms, especially those with multiple aneurysms. There are other rare causes of aneurysms such as infections of the artery wall and drug abuse, especially cocaine, which can cause the artery walls to become inflamed and weakened.

The two most common types of intracranial aneurysms are saccular or berry and fusiform. The saccular aneurysm has a general dilation of one side of the artery and accounts for most of the aneurysms. In contrast, a fusiform aneurysm is a ballooning of the entire circumference of an artery. Saccular aneurysms exhibit a variety of sizes and complex shapes; they are categorized according to neck size, location in a sidewall or at a bifurcation (see Figure 1.1A), shape, and the absolute size of the dome (the widest diameter within the aneurysm sac) as shown in Figure 1.1B.

Some aneurysms have a large absolute neck or a large neck relative to the dome size; these are categorized as wide neck. From the point of view of the endovascular surgeon, the diameter of the aneurysm neck as opposed to the dimensions of the sac is the critical factor, particularly in assessing if endovascular treatment is a viable option [Zubillaga 1994]. Even with the advances of neuro-interventional devices and techniques, wide neck aneurysms (defined as a neck diameter ≥ 4 mm or dome to neck ratio < 2 mm) [McLaughlin

2013, Wanke 2003, Kwon 2012, Parlea 1999, Zhoa 2012, Kim 2013] at a bifurcation represent a difficult subset of aneurysms to treat [Spiotta 2014, Gentric 2013, Pierot 2015]. These aneurysms occur at the junction of two essential branching arteries that must remain patent after the embolization procedure [Spiotta 2014].

Figure 1.1A – Illustration of Neck Size and Bifurcation Aneurysm

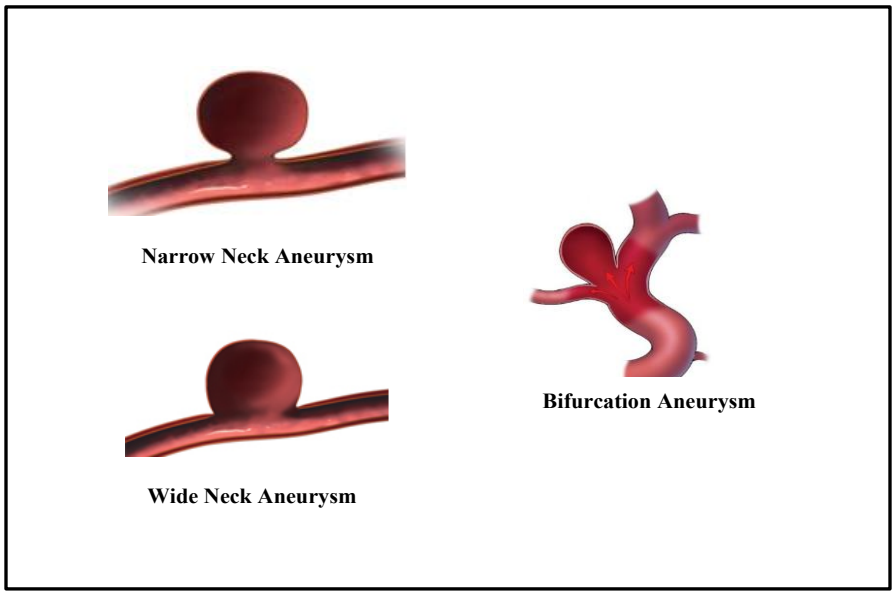
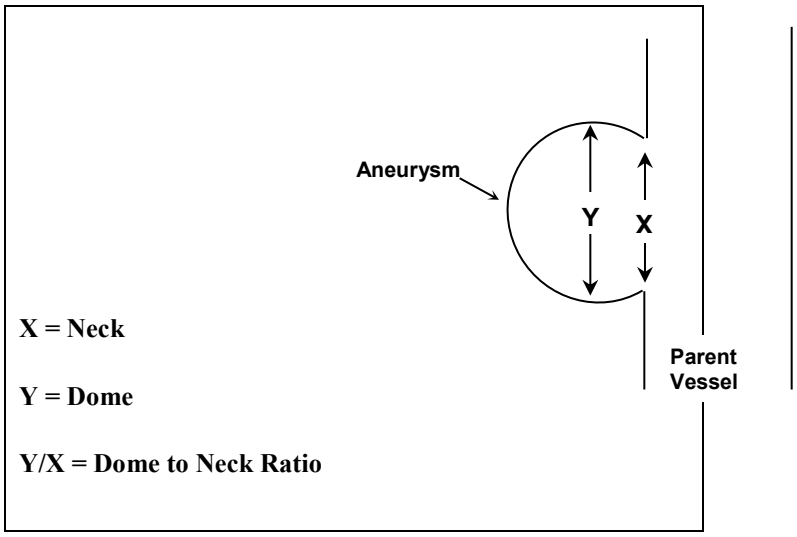


Figure 1.1B Aneurysm Sizing



Prior to the International Subarachnoid Aneurysm Trial (ISAT), which compared endovascular therapy to surgical clipping, the traditional treatment for aneurysms was open

surgery. However, open surgery is highly invasive and requires a significant recovery period even for those who are medically stable and can tolerate the procedure. In many cases, surgery may be contraindicated for patients with co-morbidities.

Following the release of the ISAT data, endovascular therapy was established as a viable alternative method for treating intracranial aneurysms [ISAT 2003, Molyneux 2005, Fiorella 2004]. Endovascular treatment is associated with fewer adverse outcomes (6.6% versus 13.2%) and decreased mortality (0.9% versus 2.5%) compared with open surgery [Higashida 2007]. However, even with current endovascular technologies some lesions are not suitable for endovascular treatment [Kato 2009]. Therefore, it is anticipated that advances in endovascular technologies will continue in order to develop effective treatment options for complex cerebral aneurysms, including wide-neck aneurysms that have been considered poor candidates for endovascular treatment. Patient selection for either surgery or endovascular coil embolization should include the risks weighed against the probability for adequate aneurysm occlusion. Other key factors to consider are aneurysm location and size, patient comorbidities, and relative contraindications e.g. allergy to contrast media, renal disease, etc. [Johnston 2002].

The concept of using a neck bridge to support coils and to improve endovascular treatment for bifurcation aneurysms was first reported in 2001 with the initial introduction of the TriSpan device (Target Therapeutics/Boston Scientific, Fremont, CA) in Europe and Canada [Raymond 2001]. More recently physicians have been treating unruptured aneurysms using stents as adjunctive devices to support the coil mass. For bifurcation aneurysms, the Y-stent technique involves the passage of a second stent through the interstices of the first deployed stent. This technique is technically demanding and requires multiple steps, each with the possibility of technical complication [Fargen 2013, Spiotta 2011, Akgul 2011]. Y-stenting has become quite prevalent for wide neck aneurysms since endovascular therapy requires high packing density as there is a relationship between aneurysm volume, packing and compaction [Sluzewski 2004]. Dense packing aids in preventing recanalization of the lesion and SAH post-procedure. However, it has been noted, that over time, about 25% of cerebral aneurysms treated with embolic coils do show evidence of some refilling of the aneurysm sac [Slob 2005] which has furthered the need for new technology. Incomplete occlusion, incomplete packing, coil compaction, or coil migration into the intra-aneurysmal thrombus may contribute to recurrence and subsequent (re)bleeding [Henkes 2005].

1.2. Current Options

The use of balloon remodeling involves the temporary inflation of a balloon across the aneurysm neck, allowing coil deployment into an aneurysm with an unfavorable dome-to-neck ratio [Spiotta 2012]. The balloon inflation can lead to local anterograde flow arrest in the territory involved. Other risks of balloon remodeling include perforator occlusion and parent vessel dissection or rupture [Cottier 2001, Shapiro 2008].

Geometrically complex aneurysms that pose a technical challenge are sometimes treated with endovascular stent assisted coiling [McDougall 1996, van Rooij 2007]. Use of a

single stent involves deploying the stent across a vessel lumen at the neck of the lesion to provide mechanical support and prevent potential coil prolapse into the vessel lumen. Y-stenting, mentioned previously, involves placing two stents in the adjacent arteries in a Y configuration [Spiotta 2017]. The disadvantages of this technique are significant and include a high risk of rupture or vessel perforation. This procedure is technically difficult and there is an increased risk of thromboembolic events due to abnormal turbulent flow resulting from the intraluminal stent overlap and lack of apposition to the vessel wall [Chow 2004, Tumialán 2008, Cho 2006]. Additionally, there is a high procedural cost and the patient must remain on long term anti-platelet medications. Based on the published literature there are ongoing efforts in the physician community to utilize current endovascular stents as makeshift neck bridges despite the documented clinical risks.

The use of current endovascular technologies in wide-neck bifurcation aneurysms can be challenging as they may not be safely deployed across the aneurysm neck without introducing abnormal turbulent flow, conformability to the vessel wall may be suboptimal, and there is potential for embolic device herniation into the parent vessel, "jailing" of adjacent vessels, and device migration. Despite advances and rapid adoption of new devices and techniques, significant unmet clinical needs still exist, creating a demand for innovation and new interventional tools for aneurysm occlusion. This is especially true for wide-neck aneurysms at a terminal bifurcation as the possibility to achieve dense packing is reduced in these lesions [McDougall 1996, Spiotta 2013].

The PulseRider was specifically designed to resolve the shortcomings of current endovascular devices that are being used to treat wide neck bifurcation aneurysms. The PulseRider device provides a bridge across the aneurysm neck and support along the vessel wall in wide-neck bifurcation aneurysms. The device has a very low metal-to-artery ratio with the majority of metal concentrated where it is needed, at the aneurysm neck to support the coil mass, rather than circumferentially. The device is delivered in a standard method through a 0.21" microcatheter, is easily recaptured and repositioned for desired placement prior to detachment and there is no need to access the daughter vessels during placement. The PulseRider supports embolic agents and may allow more dense packing of the aneurysm while preserving luminal patency and hemodynamic flow, minimizes exposed metal to encourage early device endothelialization, and securely retains embolic agents within the aneurysm sac while maintaining vessel apposition in the parent vessel bifurcation.

Although the PulseRider is specifically designed for treatment of wide-neck aneurysms at or near vessel bifurcations, the Humanitarian Use Device (HUD) classification limits treatment to carotid terminus and basilar aneurysms only. Consequently, compelling reasons still exist to expand the PulseRider indication to other intracranial aneurysms. There are currently no approved endovascular options in the US for treating all wide neck aneurysms at a bifurcation and open surgery is not always a viable option, especially for patients that are elderly or medically unstable. The PulseRider provides a treatment option for these challenging aneurysms, previously believed not appropriate for coiling, because

it is designed to provide support for the coil mass at the wide neck, prevent coil herniation, and preserve the blood flow in the daughter vessels.

Since the PulseRider has been shown to be safe and easily delivered to basilar artery aneurysms, in the more difficult to treat posterior circulation, a logical expansion of the indications would be to include middle cerebral artery (MCA) and anterior communicating artery (ACOM) artery.

The NAPA Study sponsored by Pulsar Vascular, Inc. will be a prospective, multi-center, single-arm clinical study of the PulseRider Aneurysm Neck Reconstruction Device in the minimally invasive treatment of bifurcation intracranial aneurysms. This investigational device exemption (IDE) proposes a similar study design to the ANSWER IDE study, which supported the Humanitarian Device Exemption (HDE), with the addition of the MCA and ACOM aneurysms.

1.3. Previous Experience with PulseRider Aneurysm Neck Reconstruction Device

1.3.1. Bench and Animal Studies

Bench and animal testing has been performed using the PulseRider Aneurysm Neck Reconstruction Device. Please refer to the Investigator Brochure for detailed summaries of the test protocols and corresponding reports.

1.3.2. PulseRider HDE Clinical Study

Pulsar Vascular Inc. sponsored a HDE clinical study to evaluate the safety and probable benefit of the PulseRider Aneurysm Neck Reconstruction Device under IDE G130268. The Adjunctive Neurovascular Support for Wide-Neck Aneurysm Embolization and Reconstruction Study (ANSWER) was a prospective, multi-center, non-randomized study designed to evaluate the safety of the PulseRider device in patients undergoing treatment for intracranial bifurcation aneurysms of the carotid terminus or basilar artery. Thirty-four subjects were enrolled in the clinical study at 10 clinical sites in the US.

The PulseRider is an adjunctive device to support the neck of the aneurysm and it is intended to be used with embolic coils. The device was placed at the neck of the intended target aneurysm and detached in 34/34 cases, a 100% success rate. The blinded core lab adjudicated Raymond I and II combined score was 87.9% at 180 days post-procedure. There were two secondary procedures performed during the course of the study. The HDE study was limited to basilar and carotid terminus aneurysms only and although the safety profile of the device is favorable and reported data is encouraging, a larger study in additional territories is desired.

A report of the full data set with six-month follow-up was submitted to the Food and Drug Administration (FDA) in June 2016. The HDE was approved on June 19, 2017 for use in bifurcation aneurysms in the carotid terminus and basilar arteries. Further detail on the ANSWER Study is located in the Investigator Brochure.

1.4. Rationale

The PulseRider is designed to allow for the treatment of wide-neck intracranial aneurysms at a bifurcation of the basilar artery, carotid terminus, MCA and ACOM. The PulseRider device, when used in combination with embolic agents, should enable endovascular treatment and occlusion of aneurysms that previously were untreatable or could only be treated with an open procedure. This potentially could result in higher rates of aneurysm occlusion, lower patient mortality and an acceptable rate of short-term and long-term morbidity.

1.5. Potential Risks and Benefits

1.5.1. Known Potential Risks

Risks that may be associated with the use of the PulseRider, the procedure, antiplatelet medications or general anesthesia are described in this section. Common risks (with anticipated frequency of < 20 %) include headache, dizziness, nausea and vomiting, groin injury or hemorrhage, pain at the insertion site, or insertion site hematoma/bleeding. All other risks are uncommon or rare and are expected to occur with frequency < 10% [Naggara et al. 2010].

Table 1.5.1A Anticipated Risks

Common risks with anticipated frequency of < 20%	
Dizziness	Insertion site hematoma/bleeding
Groin injury or hemorrhage	Nausea and vomiting
Headache	Pain at insertion site
Uncommon or rare risks with anticipated frequency of < 10%	
Adverse reaction to antiplatelet/anticoagulation agents	Hypertension
Adverse tissue reaction	Hypoesthesia
Allergic reaction and anaphylaxis from device and contrast media	Hypotension
Allergy to nickel	Hypothermia
Allergy to nitinol	Incomplete aneurysm occlusion
Aneurysm perforation or rupture	Increase in intracranial pressure
Aneurysm recanalization or regrowth	Infarction
Arteriovenous fistula	Infection including urinary tract infection
Blurry vision	Infection at insertion site
Cardiac arrhythmia	Intracerebral hemorrhage
Cardiac failure	Intracranial hemorrhage
Cerebral edema	Ischemia
Cerebral infarct	Laboratory abnormality
Coagulopathy	Mass Effect
Cognitive impairment	Myocardial infarction
Coil migration	Neurological deficits
Coil prolapse or herniation into normal vessel through or around device	Perforation
Coma	Perforator occlusion

Confusion	Phlebitis
Cortical blindness	Pneumonia
Cranial nerve deficit(s)	Post-procedure bleeding
Cranial nerve palsy	Pseudo-aneurysm formation
Death	Renal failure
Deep vein thrombosis	Retroperitoneal hematoma
Device delivery failure	Ruptured or perforated vessel or aneurysm
Device deployment difficulty	Seizure
Device fracture	Stenosis or occlusion within the device
Device migration	Stenosis or occlusion of parent vessel
Device misplacement	Stenosis or occlusion of perforator
Diplopia	Stenosis or occlusion of side branch
Dissection	Stenosis or occlusion of treated segment
Disseminated intravascular coagulation	Stroke
Ecchymosis	Thromboembolism
Edema	Tissue necrosis
Emboli (air, tissue, thrombotic and device)	Transient ischemic attack (TIA)
Embolic stroke	Vasospasm
Emergent neurosurgery	Vessel dissection
Facial numbness	Vessel occlusion
Fever	Vessel perforation
Fracture of delivery wire	Vessel thrombosis
Hematoma	Visual field deficit
Hemorrhage	Vision impairment
Hydrocephalus	Weakness left or right side

1.5.2. Minimization of Risk

Efforts will be made to minimize the potential risks through the following:

1. Investigators who participate in the study will be experienced and skilled in neuro-intervention surgery and will have adequate resources to conduct the clinical study.
2. The study has been designed to ensure treatment and follow-up of subjects are consistent with current medical practice.
3. Each investigator will ensure oversight and approval of the study by the IRB prior to initiation of the study at the investigation site.
4. The investigator and study personnel will be trained on the study protocol.
5. The investigators and appropriate personnel will undergo training on the use of the PulseRider device prior to first use during the study.
6. Subjects will be carefully evaluated against the inclusion/exclusion criteria prior to being enrolled in the study to ensure that their diagnosis and medical status are appropriate for participation.
7. Subject status will be monitored by the investigator or designee throughout the follow-up period as defined in the study protocol.

8. The investigator or designee will evaluate the subject for any adverse events potentially related to the procedure or to the device. Device status will also be assessed using appropriate imaging modalities defined in the study protocol.
9. All reportable adverse events for the study will be reviewed and adjudicated by a CEC.
10. Data from all investigation sites will be monitored throughout the study to evaluate protocol compliance and identify any issues that may affect the safety and welfare of the subjects.
11. De-identified angiograms will be reviewed by an independent core laboratory to assess PulseRider device placement and occlusion of the aneurysm. Sites are requested to provide de-identified images to the core lab. In the event, images are received with any patient identifiers, the core lab's proprietary software removes all patient protected health information (PHI) as images are processed through their system. Each image is then reviewed by a radiology technician to ensure that all PHI was adequately removed. This two-fold process is completed before image exam is uploaded and reviewed. The radiology technician/assessor will also be blinded to the subject's previous medical history.

1.5.3. Known Potential Benefits

The potential benefits of the PulseRider device are that it may decrease or stop the blood flow into the aneurysm and thus decrease or eliminate the symptoms that the aneurysm is causing (if any) or decrease or eliminate the chance of future aneurysm rupture which often leads to stroke or death. The specific benefits of the device include that it may be a safer and faster procedure than currently used methods to treat bifurcation aneurysms and it may be possible to treat patients whose aneurysms previously could not be treated or have been incompletely treated with other techniques (e.g. previously placed coils). By changing the flow in the blood vessel and aneurysm, it is hoped that the PulseRider device will lead to a more lasting cure of the aneurysm. Although there may be no direct benefits of study participation, subject participants will undergo an enhanced level of clinical scrutiny compared to routine clinical care, which may provide some indirect health benefits. The potential benefits of the device outweigh the anticipated risks.

2. Objectives and Purpose

2.1. Objectives

The primary objective of this study is to determine the safety and efficacy of the PulseRider as an adjunctive therapy in conjunction with coil embolization in the minimally invasive endovascular treatment of intracranial aneurysms at a bifurcation of the basilar artery, carotid terminus, MCA, and ACOM. The data will be generated under an IDE and will be used to support a Pre-market Approval Application.

3. Study Design and Endpoints

3.1. Description of the Study Design

This study is designed as a prospective, multi-center, single-arm investigation of the PulseRider Aneurysm Neck Reconstruction Device used in conjunction with coil embolization in the treatment of unruptured wide-neck bifurcation intracranial aneurysms of the basilar artery, carotid terminus, MCA and ACOM. Up to 160 evaluable subjects will be enrolled at up to 28 clinical sites throughout the United States.

For this study, a single-arm design is deemed appropriate as there are currently no approved comparator devices indicated for the treatment of wide-neck bifurcation aneurysms available in the US. Subjects with unruptured, angiographically confirmed wide-neck (≥ 4 mm or a dome-to-neck ratio < 2) intracranial aneurysms located at the bifurcation of the basilar artery, carotid terminus, MCA and ACOM arising from the parent vessel for the target aneurysm with a diameter of 2.0 mm to 4.5 mm will be enrolled and expected to be followed through five year post-procedure.

3.2. Study Endpoints

3.2.1. Primary Endpoint - Safety

Composite of Neurological Death or Major Ipsilateral Stroke (in downstream territory) up to 1 year post-procedure:

> **Stroke** is defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours with no apparent cause other than of vascular origin, including ischemic stroke and/or hemorrhagic stroke (i.e., intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EDH)) [Hatano 1976].
>
> **Major Stroke** is defined as stroke with symptoms persisting for more than 24 hours AND a sudden increase in the NIHSS of the subject by > 4.
>
> **Minor Stroke** is defined as stroke with symptoms persisting for more than 24 hours and a sudden increase in the NIHSS of the subject by 1-3.
>
> **TIA** is defined as stroke symptoms resolving within ≤ 24 hours.

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

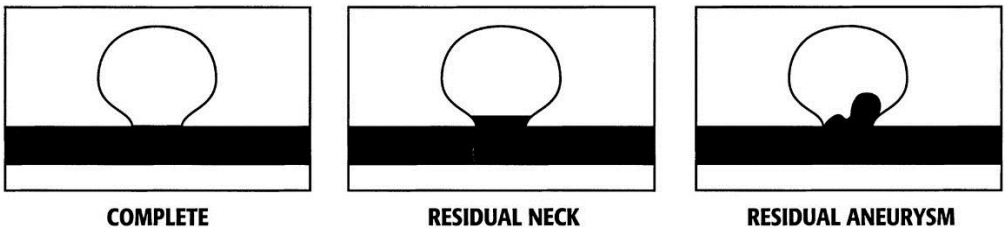
3.2.2. Primary Endpoint - Effectiveness

Complete Occlusion:

Rate of complete aneurysm occlusion (Raymond I) without significant parent artery stenosis (> 50% stenosis) or prior retreatment at 1 year post-procedure.

The aneurysm occlusion and parent artery stenosis assessments in this endpoint will be evaluated by the independent core laboratory. Retreatment will be reported by the site.

Figure 3.2.2A Raymond Scale [Roy 2001]



- **Class I: Complete** = Complete obliteration
- **Class II: Residual Neck** = Persistence of any portion of the original defect of the arterial wall but without opacification of the aneurysmal sac
- **Class III: Residual Aneurysm** = any opacification of the aneurysm sac

3.2.3. Secondary Endpoints - Effectiveness

The secondary effectiveness endpoints are pre-specified below and have been identified as outcomes meaningful to evaluate the effectiveness of aneurysm treatment with a device that is an adjunct to embolic coiling.

- Technical Success is defined as successful implantation of device— physician able to access target aneurysm, deploy PulseRider device at the neck of aneurysm and device was detached successfully. This endpoint will be reported by the investigator.
- Ability to retain embolic coils within aneurysm immediately post-procedure. This endpoint will be evaluated by the independent core laboratory.
- Complete aneurysm occlusion at 3 years and 5 years.
- Adequate aneurysm occlusion (defined as Raymond I and II combined) at 1 year, 3 years and 5 years.
- The percentage of target aneurysms that are retreated through 1 year, 3 years and 5 years. Retreatment will be reported by the investigator.
- The percentage of subjects with significant stenosis defined as > 50% at implant site at 1 year, 3 years and 5 years. This endpoint will be evaluated by the independent core laboratory.
- The percentage of subjects with mRS 0 – 2 at 1 year, 3 years and 5 years.

3.2.4. Additional Endpoints

- The percentage of target aneurysm rupture up to 1 year, 3 years and 5 years. This endpoint will be evaluated by the independent core laboratory.
- No migration (defined as ≤ 2mm) of the device at 1 year, 3 years and 5 years. This endpoint will be evaluated by the independent core laboratory.

4. Study Population

4.1. Participant Inclusion Criteria

Investigators will assess potential subjects who are candidates for the study. In addition, an image of the subject's aneurysm and branch arteries must be reviewed and approved by the Image Screening Committee. Candidates who meet the protocol inclusion/exclusion criteria with at least one bifurcation intracranial aneurysm that is acceptable for minimally invasive treatment and approved by the Image Screening Committee may be enrolled. The subject selection criteria are in place for protection of participants and to address factors that may compromise the outcome of the investigation or interpretation of the results.

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

1. Subject with an angiographically confirmed digital subtraction angiogram (DSA) or computed tomography angiogram (CTA) of wide neck (≥ 4 mm or dome to neck ratio < 2) intracranial aneurysm located at a bifurcation of the basilar artery, carotid terminus, MCA or ACOM
2. The parent vessel for the target aneurysm has a diameter of 2.0 mm to 4.5 mm
3. The subject is between 18 and 80 years of age the time of consent
4. Informed consent is obtained and the subject signs the Institutional Review Board (IRB) approved consent prior to beginning any study procedures along with the HIPAA Authorization for the release of PHI
5. In the opinion of the treating physician, placement of the PulseRider device is technically feasible and clinically indicated
6. Subject has the mental capacity, willingness and ability to comply with protocol requirements and follow-up through 5 years for the clinical study

4.2. Participant Exclusion Criteria

Candidates will be excluded from participation if ANY of the following apply:

1. Unstable neurological deficit (condition worsening within the last 90 days)
2. Subarachnoid Hemorrhage within the last 60 days
3. Irreversible bleeding disorder
4. Modified Rankin Score (mRS) score ≥ 3
5. Patient has another intracranial aneurysm that in the Investigator's opinion, may require treatment within the 1 year follow up period
6. Patient has previously had two or more (≥ 2) procedures to treat the target aneurysm
7. Patient with an untreated target aneurysm that is partially thrombosed
8. Platelet count < 100 x 10^3 cells/mm^3
9. Inability to tolerate, adverse reaction to or any contraindication to taking aspirin or P2Y12 inhibitor

10. A history of contrast allergy that cannot be medically controlled
11. Known allergy to nickel
12. Relative contraindication to angiography (e.g., serum creatinine > 2.5 mg/dL)
13. Woman of child-bearing potential who cannot provide a negative pregnancy test
14. Evidence of active systemic infection (e.g. fever with temperature > 38°C/100.4°F and/or white blood count (WBC) > 15,000)
15. Conditions that carry a high risk of neurological events or stroke (e.g., uncontrolled hypertension, prior ischemic stroke, Moya moya disease).
16. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 5 year follow-up period
17. Vessel tortuosity or stenosis that prohibits safe endovascular access to the target aneurysm to allow for treatment with the study device
18. Current involvement in a study for another investigational product
19. Patient and /or family considering a move from this geographical location at the time of consent
20. Categorized as a vulnerable population and require special treatment with respect to safeguards of well-being (e.g. cognitively impaired, veteran, prisoner, etc.)

4.3. Strategies for Recruitment and Retention

The study will enroll a total of 160 subjects in the United States at up to 28 clinical sites. Once enrolled, each subject will participate in the study for 5 years post-procedure. A recruitment packet, that can be customized, may be provided to each clinical site. The packet may include a sample email/letter to referring physicians, a slide deck explaining the clinical study for presentation at grand rounds or other meeting of referring physicians and a patient information booklet describing the device, the indications, the clinical study and the necessary commitment to completing all study visits.

The Sponsor's intention is for the enrolled subject population to be as representative as possible of the well-defined study population. Investigators will be encouraged to evaluate all unruptured and bifurcation aneurysm patients for participation in the study, and to offer enrollment to all who meet preliminary eligibility criteria.

Clinical sites will be selected for participation in the study based on experience with similar stenting technologies, ample unruptured bifurcation aneurysm patient population, the capacity to screen and enroll a reasonable number of eligible patients, and the ability to perform the required study procedures, per this protocol. Sponsor will attempt to include a diversified group of investigational sites engaging a variety of academic and private institutions geographically located throughout the US. To ensure generalizability of results and minimize the influence of any single site, no more than approximately 20% of the total

enrollment will be allowed at a single site (i.e., a maximum of 32 subjects enrolled per site).

In order to enhance participant retention and compliant follow-up visits, site coordinators will be encouraged to schedule their subject follow-up visits early in the visit windows with ample opportunity to reschedule as needed, before the visit window closes.

4.4. Participant Withdrawal or Termination

4.4.1. Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time upon request. The investigator may terminate participation in the study if any adverse event or other medical condition or situation occurs such that continued participation would not be in the best interest of the participant. A subject may be terminated if they meet an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.4.2. Handling of Participant Withdrawals or Termination

Subjects that withdraw consent after treatment are not required to undergo follow-up after withdrawal. They will not be replaced and will be considered part of the subject cohort. The reason for early withdrawal will be documented in the source documents and case report forms.

In the event a subject withdraws from the study, their data will be excluded from the data analysis from the time of withdrawal going forward. All data collected prior to withdrawal will be included in the data analysis.

5. Study Device

5.1. Study Device Description

5.1.1. Device Acquisition

The PulseRider investigational device is manufactured by Pulsar Vascular, Inc., in Los Gatos, California. The device will be provided to the clinical study sites by the Sponsor, Pulsar Vascular, Inc. after obtaining the fully executed clinical study agreement and IRB approval at each site.

5.1.2. Device Appearance, Packaging, and Labeling Description

The PulseRider Aneurysm Neck Reconstruction Device is a self-expanding nitinol implant designed to retain embolic coils within an aneurysm occurring at a vessel bifurcation. The PulseRider is comprised of the torque device, delivery wire, introducer, and implant.

There are three defining attributes of the implant: shape, arch width and parent vessel diameter. The PulseRider is available in T and Y shapes (see Figure 5.1.2A) with 8 mm and 10 mm wide arches. The anchor base is available in sizes to treat parent arteries from 2.0 mm to 4.5 mm. Depending on the size of the aneurysm neck and parent vessel, the appropriate size PulseRider implant must be chosen to ensure adequate stability and

anatomical fit. Figure 5.1.2B illustrates the implant placed in a vessel bifurcation supporting embolic coils.

Figure 5.1.2A. PulseRider T and Y Shapes

There are three defining attributes of the implant: shape, arch width, and parent vessel diameter.

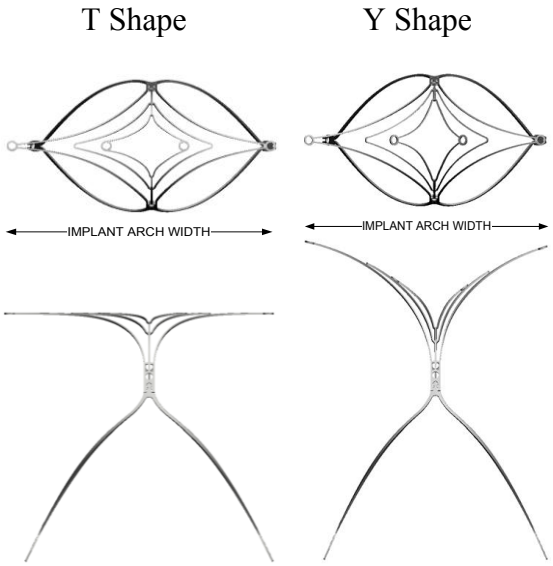
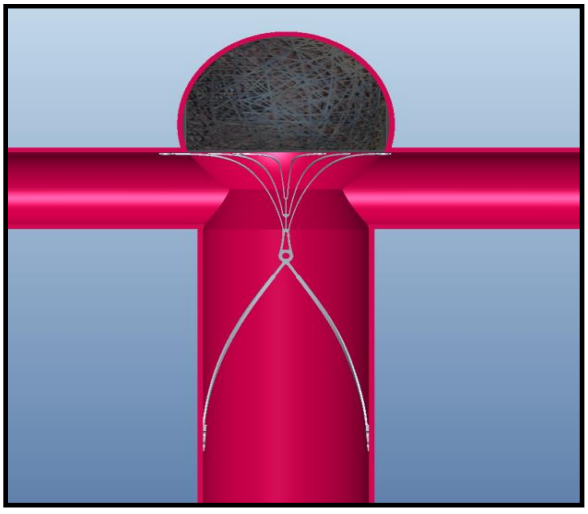


Figure 5.1.2B. Implant Placed at a Vessel Bifurcation and Retaining Embolic Coils



The PulseRider device shall be placed according to the IDE Instructions for Use (IFU) using standard endovascular techniques. The IFU is packaged with each investigational device. The unique open cell frame configuration conforms to the vessel walls with a profoundly patent lumen profile. The device is retrievable and may be repositioned by retracting into the microcatheter at any time during or after deployment, but prior to detachment. The implant is deployed at the parent vessel bifurcation and across the aneurysm neck to provide a supporting framework, bridging the aneurysm neck while retaining embolic agents within the aneurysm. Platinum and radiopaque markers are located at the proximal end, the middle, and the distal tips for fluoroscopic visualization during placement.

5.1.3. Device Training Requirements and Investigator Experience

In addition to the clinical protocol training, all investigators who will be performing procedures for this study will be required to undergo training via a device in-service, which includes detailed reviews of the PulseRider IFU and device (specifications, indications for use, procedural components, etc.) as well as benchtop training under fluoroscopy. A proctored first case or prior human case experience is required. The combination of the didactic and hands-on portions of the device training will document and provide the investigator with the experience necessary to perform the protocol specified procedures for the study.

PulseRider should only be used by investigators who have received appropriate training in interventional neuroradiology and the treatment of intracranial aneurysms. Additionally, only the attending treating physicians who have completed device training will be able to perform the placement of the PulseRider and coils in the study procedure.

5.1.4. Device Storage and Stability

The PulseRider device should be stored in a cool dry place. Devices are to be stored in a secure location and in accordance with the IDE IFU. Do not use this device after the "Use By" date.

5.1.5. Device Preparation

Detailed preparation instructions for the PulseRider device are provided in the IDE IFU.

5.1.6. Instructions for Use

A comprehensive IDE IFU for the PulseRider is available with each device.

5.1.7. Specific Considerations

In addition to the PulseRider, the following commercially available items are required for the procedure and will be provided by the site:

- An electrolytic detachment power supply (refer to the power supply Directions for Use)
- Fresh batteries for the power supply for each procedure
- A second power supply to be used as back-up

- One non-tapered 6F (2.0 mm) guide catheter with a 90 cm minimum effective length
- A continuous flush setup including two rotating hemostasis valves (RHVs), heparinized saline, one 3-way stopcock, and one 1-way stopcock
- One sterile 20 gauge (0.9 or 0.7 mm) uncoated stainless steel hypodermic needle to provide electrical ground during implant detachment. (Warning: DO NOT use Teflon coated needles)
- Alcohol-dampened gauze to clean delivery wire proximal end before connecting power supply detachment cable

5.1.8. Duration of Implant Exposure

The PulseRider is a permanent implant. In the event the PulseRider device needs to be removed during the course of a procedure for any reason, i.e. wrong size or shape, device malfunction or device failure, the PulseRider shall be returned to Pulsar Vascular, Inc. per standard institutional practices for biohazard waste. Please refer to Section 5.1.10 regarding complaint handling.

5.1.9. Investigational Device Accountability

Access to investigational device will be controlled and thorough records of investigational devices shipped to each site will be maintained by the Sponsor and investigator. Study devices will be labeled as 'Investigational Device' and are only to be used for subjects enrolled in this clinical study. Investigational devices will be shipped to the clinical sites upon completion of required documentation and as necessary to treat enrolled subjects.

The investigator is responsible for device accountability at the study site. The investigator may assign device accountability to an appropriate staff member who must be listed on the Delegation of Authority Log.

It is the responsibility of the Investigator to ensure that:

- All study devices received are inventoried and accounted for
- The disposition of each device is recorded
- The investigational device will not be supplied to any person except those named as sub-investigators on the Delegation of Authority Log
- The investigational devices are used in accordance with the IDE IFU and study protocol
- Only subjects enrolled in the study will be treated with the investigational device
- The investigational devices are stored in a secured storage facility to which only the investigator or designated personnel will have access.

Authorized study personnel will maintain device accountability records. Upon receipt of the study devices, the shipment will be inventoried to ensure the information on the packing slips matches what has been sent to the site. A copy of shipping documents and packing slips shall be filed in the site regulatory file. The device accountability log shall be

maintained throughout the study including information such as the person in receipt of devices, date received, quantity received, lot numbers, expiration date, implant date, subject ID, and device disposition/date. Traceability shall be achieved during and after the clinical investigation through device lot numbers and accurate accounting records.

One PulseRider device will be implanted per subject treated in the study for an anticipated total of 160 devices implanted. The PulseRider is a single use device and one PulseRider is used to treat a single aneurysm.

5.1.10. Device Returns

Unused investigational devices being reclaimed for excess inventory, following study completion or due to product expiration, damage, or defect should be returned to Pulsar Vascular, Inc. or designee. Opened and unused devices should also be returned to the Sponsor. Any suspected device malfunction, treatment failure or device associated with an adverse event (device related or possibly device related) will undergo a thorough complaint analysis and must be properly documented on the Electronic Case Report Forms (eCRFs). In the event of a suspected malfunction or device observation, the device shall be returned to Pulsar Vascular, Inc. for analysis if the device was not implanted. All returned devices must be properly decontaminated per hospital policy and properly labeled with the subject identification number, date of event, identified as a defective return, non-defective return, or adverse event. Retain tracking information. All investigational devices should be returned to:

ATTN: Complaints

Pulsar Vascular, Inc.

130 Knowles Drive, Suite E

Los Gatos, CA 95032

6. Study Procedures and Evaluation

6.1. Study Procedures and Evaluations

6.1.1. Study Specific Procedures

The procedures that are study specific and not part of standard care for treatment of intracranial aneurysms include a pre-procedure pregnancy test for pre-menopausal women and placement of the PulseRider device at the aneurysm neck.

6.1.2. Standard Care Procedures

Most of the procedures completed as part of this study are standard practice and include relevant medical history, relevant medication history, complete blood count, blood coagulation tests, neurological examination, NIHSS, mRS, DSA, CTA, MRA, review of any adverse events and review of relevant concomitant medications. This may vary from site to site.

6.2. Laboratory Procedures/Evaluations

6.2.1. Clinical Laboratory Evaluations

Clinical laboratory evaluations will include a complete blood count, serum creatinine, anticoagulation tests, and a pregnancy test, if applicable.

6.2.2. Other Procedures – Angiograms

A DSA will be done immediately prior to the PulseRider placement. Selection of the artery and angiography will follow standard techniques. This image evaluation is done to define the size and shape of the aneurysm, to note how the PulseRider is intended to be placed and to confirm that the subject remains eligible for the study and a candidate for PulseRider placement. A DSA will be taken immediately post-implantation of the device to evaluate placement success, and a DSA will be taken at the conclusion of the procedure to evaluate occlusion.

6.2.3. Core Laboratory for Image Evaluation

An independent radiographic core laboratory shall be utilized to provide an unbiased and standardized assessment of all imaging. All subject PHI will be removed before an image is uploaded and evaluated. The core lab assessor will be blinded to subjects' previous medical history. The core lab will evaluate the following:

- Aneurysm and vessel dimensions
- Ability to retain embolic coils without coil protrusion/herniation (yes/no)
- Aneurysm occlusion: evaluated per the Raymond– Roy scale referenced in Section 3.2.2
- Parent and branch vessel stenosis: evaluated on a scale of 0-50% and > 50-100%
- Device migration: migration is defined as > 2mm

All imaging shall be performed in accordance to the core laboratory recommended protocol provided to the sites. A copy of the study angiograms will be submitted to the core lab.

6.2.4. Angiogram Shipment

De-identified images may be sent via DICOM format on a CD (that contains the subject ID, study visit, Sponsor name, and protocol number), or electronically to the core lab website, if available.

6.3. Concomitant Medications, Treatments, and Procedures

Dual anti-platelet medications will be reviewed and updated at each visit and changes will be recorded in the electronic data capture (EDC). Other concomitant medications to be recorded include anti-hypertensives, sedatives, hypnotics, hemolytic modifiers, anticoagulant medications, antibiotics and any other medications to treat neurological adverse events.

6.4. Prohibited Medications, Treatments, and Procedures

If a subject has more than one aneurysm, the one not being treated with a PulseRider device should be treated first prior to the subject's enrollment in the study or the treating physician should document that he/she believed in his/her best judgment the non-PulseRider aneurysm is unlikely to need treatment within one year of the PulseRider procedure.

6.5. Prophylactic Medications, Treatments, and Procedures

Dual anti-platelet medication is required and should be initiated prior to the PulseRider procedure. The antiplatelet and anticoagulation regimen used for interventional intracranial procedures as part of this study is at the discretion of the treating physician. Each center will provide the standard dual anti-platelet therapy regimen followed at their institution to Pulsar Vascular, Inc.

7. Study Schedule

7.1. Screening

During the initial screening phase, the investigator will perform an initial evaluation of potential study subjects for study eligibility. This initial screening phase may include review of existing patient information (e.g. previously performed angiography, radiographs, laboratory studies, medical history, physical examination, etc.) For subjects who meet the eligibility criteria and agree to participate, informed consent will be obtained and the informed consent form will be signed. Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's study participation. The investigator, or designee, will explain the research study to the patient and answer any questions that may arise. The possible risks and possible benefits of participation will be discussed. The patient will be asked to read, review and sign the IRB-approved consent form. Informed consent is mandatory and must be obtained from all subjects prior to their participation in the study. The informed consent process is detailed further in Section 11.3.

All patients *who provide written informed consent* will be entered into EDC regardless of whether or not they participate in the study.

7.2. Enrollment, Baseline Evaluation, and Procedures

7.2.1. Pre-Procedure/Baseline Assessments

The following baseline data will be collected and assessments performed after providing informed consent and prior to the index procedure.

- **Baseline anti-platelet medication** will be administered using a regimen that is according to the investigators standard of care anti-platelet regimen.
- **Relevant medical history** will be collected from a subject interview and a review of the subject's medical records with specific attention to neurological deficits/sequelae, bleeding disorders, cardiac conditions that carry a high risk of neurological events, or conditions that may compromise survival or ability to complete follow-up.

- **Relevant medication history** will be collected from a subject interview and a review of the subject's medical records if necessary. Antithrombotic (including anticoagulants and fibrinolytics), inhibitors of ADP-induced platelet aggregation medications, anti-hypertensives, sedatives, hypnotics and any medication used to treat neurological events the subject has taken within 7 days prior to the index procedure will be recorded. Dual anti-platelet therapy (DAPT) will be collected within 30 days prior to the index procedure.
    - Please note that only the following medications should be recorded in the Medication Log eCRF:
        - DAPT
        - Anti-hypertensives
        - Sedatives
        - Hypnotics
        - Hemolytic modifiers
        - Antiplatelet and anticoagulant medications
        - Antibiotics
        - Any other medications to treat adverse events collected in this study
- **Clinical laboratory tests** will include a complete blood count, serum creatinine, and blood coagulation tests. Subject laboratory values will be screened against the exclusion criteria for study eligibility.
- **A pregnancy test** will be done immediately before the procedure, if applicable. Pregnancy may also be ruled out by medical history (e.g. menopause, surgical sterility).
- **Neurological exam** – A standard neurological exam includes evaluations of cerebral function, cerebellar function, motor and sensory function, reflex function, gait and stance, and cranial nerve function. The neuro exam will be performed by qualified personnel.
- **National Institutes of Health Stroke Scale – NIHSS**. The NIHSS is a standardized clinical assessment tool that provides a quantitative measure of stroke-related neurologic deficit. It is widely used to evaluate stroke severity, determine appropriate treatment, and predict patient outcome. The NIHSS will be performed by qualified personnel. All study personnel performing the NIHSS assessment will be required to have training on the administration of the NIHSS assessment. A valid certification of completion of training will be stored in the site study files.
- **Modified Rankin Scale – mRS**. The mRS is a scale commonly used to measure the degree of disability or dependence in the daily activities in patients following stroke or other neurologic event and is conducted by qualified personnel. It is a scale with six categories ranging from no symptoms to severe disability and death. All study personnel

performing the mRS assessment will be required to have training on the administration of the mRS assessment. Documentation of completion of training will be stored in the site study files and updated at least every 2 years.

- **Baseline aneurysm imaging evaluation**. The baseline imaging evaluation may be a DSA or CTA. The baseline imaging must be reviewed and approved by the Image Screening Committee. As the status of the target aneurysm may change between the baseline image and procedure, a DSA is required prior to enrollment on the procedure day to confirm that the subject remains eligible for the study.
- **Image Screening Committee.** During initial subject screening, the site will submit a de-identified image (either DSA or CTA) to the core lab. Core lab personnel will submit the de-identified baseline image to the Image Screening Committee who will review the image for approval or disapproval. The decision of the committee will be based on their review of the appropriateness as outlined in the Image Screening Committee charter. Upon decision from the Image Screening Committee, the site will be informed of the subject approval/disapproval.

The schedule of assessments is listed in Table 7.15A. The baseline imaging must be completed within 180 days of the index procedure. All baseline tests should be completed within 60 days prior to the device placement procedure. This 60 days is inclusive of the procedure day, prior to the index procedure. The NIHSS, mRS, pregnancy test (if required), and the imaging study confirming anatomic eligibility criteria are required on the day of the index procedure

Final eligibility cannot be determined until the immediate pre-procedure DSA is completed. This takes place immediately prior to the index procedure and it is expected that some subjects may be excluded at that time. Excluded subjects will undergo routine clinical care for their aneurysm treatment and will be considered a screen failure for the study.

A patient is considered enrolled in this study after the patient is consented, approval of imaging screening committee is received, pre-procedure angiogram is completed and the treating physician confirms the subject meets all eligibility criteria on the day of the study procedure.

7.3. Treatment

The subject should be prepared for the planned interventional procedure according to standard hospital procedures.

Peri-procedural heparin will be administered according to the institutional standard of care protocol. Dual anti-platelet therapy will be administered prior to and post-procedure according to the institutional standard of care.

Immediately prior to PulseRider placement, the physician will perform a DSA of the affected intracranial arteries. Selection of the artery and DSA will be done using standard techniques. The purpose of the pre-procedure angiogram is to define the size and shape of

the aneurysm and bifurcation arteries, to note how the PulseRider is intended to be placed and to confirm that the subject remains a candidate for PulseRider placement and study eligibility.

The PulseRider device will be used according to the IDE IFU.

A DSA will be taken immediately after implantation of the PulseRider device to evaluate placement success. The DSA will be repeated at the conclusion of the procedure to evaluate occlusion. The procedure images will provide a pre-treatment and post-treatment comparison.

7.4. Procedure Assessments

Index procedure start/end times will be recorded and the following definitions apply to the index procedure:

- Procedure start time is defined as the point when the guiding catheter is introduced into the subject.
- Procedure end time is defined as the time the last catheter is removed from the subject.

Procedural assessments – pre-treatment, intra-treatment and post-treatment include:

- Procedural medications
- Event assessment
    - Adverse events
    - Protocol deviations
    - Device malfunctions/deficiency
    - Angiogram
    - Post-treatment aneurysm occlusion per Raymond– Roy scale
    - Send the pre-treatment, intra-procedure, and post-treatment DSA to the core lab

At a minimum, the following data will also be captured during the procedure:

- Name of the implanting physician
- Aneurysm and vessel dimensions
- PulseRider device implanted
- Device implant success
- Adjunctive devices used including coils and balloons
- Ancillary devices used including the microcatheter
- Fluoroscopy time

- Presence of vasospasm (vessel and times of onset/resolution). Vasospasm will be captured as an adverse event only if it leads to a subsequent thrombotic or ischemic event.

7.5. Procedural and Post-Procedural Medications

All vasoactive and anticoagulant medications that were administered intra-procedurally until the end of the index procedure will be recorded.

Post-procedural medication collection will include the following medications:

- DAPT
- Anti-hypertensives
- Sedatives
- Hypnotics
- Hemolytic modifiers
- Antiplatelet and anticoagulant medications
- Antibiotics
- Any other medications to treat adverse events collected in this study

7.6. Follow-up in the Event of Stroke or Suspected Stroke

If a subject experiences a stroke, or if there is any symptom or suspicion of a stroke, in addition to the hospital/physician routine standard of care for stroke, the following instructions apply:

1. Obtain Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) if indicated within 24 hours after the onset of symptoms.
2. Contact the Sponsor about the event.
3. Complete the stroke specific AE form and perform the neurological exams, NIHSS and mRS.

In the event that the subject experiences a stroke but the investigator did not learn of the stroke at the time it occurred, and if a MRI was not done, the investigator should obtain a MRI as soon as possible upon learning of the stroke, and complete steps 2-3 above.

7.7. Post-Procedure Follow-up

The follow-up period begins immediately post-treatment. Site personnel will review the follow-up requirements with the subjects to help ensure compliance with the schedule. Follow up assessments occur at the following timepoints after the index procedure and are listed in Section 7.15:

- At the time of hospital discharge

- 30 days +/- 7 days
- 180 days +/- 42 days
- 1 year +/- 60 days
- 2 years +/- 60 days
- 3 years +/- 60 days
- 4 years +/- 60 days
- 5 years +/- 60 days

The assessments to be completed at each in-office post-procedure follow-up are listed in Section 7.15 and include:

- Neurological exam
- National Institutes of Health Stroke Scale – NIHSS
- Modified Rankin Scale – mRS
- Imaging
  - Any imaging performed (DSA, MRA, CTA) per standard of care after the study procedure and prior to the final visit will be collected.
  - **DSA is required at the 1 year follow-up visit**
  - DSA or MRA is required at the 3 and 5 year follow-up visits
- Review of relevant medications
- Review of adverse events

The assessments to be completed at the telephone follow-up are listed in Table 7.15A and include an evaluation of any potential adverse events, a review of the medications taken (particularly anti-platelet medication) and mRS. For the mRS, note in source documents that the questions and assessment were done via telephone.

It is important that the follow-up schedule be adhered as closely as possible for all subjects. Subjects may not be able to return for visits at exactly the date required therefore, a visit window is acceptable and is provided in Section 7.15. Visits not completed within the window will be recorded as protocol deviations. A study visit should be scheduled as close as possible to the earlier side of the visit window to allow for possible re-scheduling thereby minimizing deviations.

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment and to reschedule. The reason for the missed visit shall be recorded. If the missed visit was due to an AE, an AE eCRF must be completed and any reporting and assessment requirements must be met.

7.7.1. Medical Resource Utilization and Health Economics (HECON)

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Procedure and post-procedure healthcare resource utilization will be assessed at hospital discharge and at all scheduled post-procedure visits. Healthcare resource utilization will include length of hospitalization, re-hospitalization or prolongation of hospitalization, and unscheduled clinical visits for aneurysm treatment follow-up.

7.7.2. Study Participation and Information Card

The incidence of missing data can compromise any clinical study. In an effort to retrieve all clinical data, even for evaluation(s) and therapy outside of the treating hospital or department, subjects enrolled in this study will be provided with a "Study Participation and Information Card."

Prior to discharge subjects will be counseled to provide a copy of this card when visiting any physician other than the interventional neuro-radiologist at the clinical site. This wallet size card will include a request for the study investigator to be notified of any hospital admission and/or an evaluation for anything neurological in nature, whether or not it involves hospitalization. If such an event takes place, the study investigator will be instructed to request other physician(s) not on the study team to conduct an NIHSS assessment when a study subject sees the physician for a non-study visit and to provide this data, along with any other relevant data collected as a part of standard of care during the visit (e.g. adverse events, mRS, neurological exam, imaging studies, etc.) to the study investigator's site.

7.8. Follow-up Angiography

Any imaging performed (DSA, MRA, CTA) per standard of care after the study procedure and prior to the final study visit will be collected. **A DSA is required at the 1 year follow-up.** Either DSA or MRA is required at the 3 year and 5 year follow-up visits. The intent is to evaluate aneurysm occlusion and the PulseRider implant. The Investigator will grade aneurysm occlusion according to the Raymond Scale. Should any imaging be considered necessary at a non-study required time point, it is requested that an assessment of the treated aneurysm be performed and the appropriate eCRF including a reason for the unscheduled procedure should be completed. Any imaging performed as standard of care will be collected and sent to the core lab.

7.9. Final Study Visit

The final study visit should be done at 5 years (+/- 60 days) following the PulseRider procedure. A DSA or MRA will be performed and all other post-procedure assessments will be completed. Any ongoing AE/SAEs should be reviewed, assessed for resolution and any documentation completed. Upon exit from the study, the subject will undergo standard follow-up with their doctor and data will not be collected.

7.10. Unscheduled Visit

Subjects returning for an unscheduled visit indicating new or unresolved signs and/or symptoms will be documented as an unscheduled follow-up and, at the investigator's discretion, be reported as an adverse event. Information to be collected, at a minimum includes:

- Neurological exam
- National Institutes of Health Stroke Scale – NIHSS
- Review of relevant medications
- Review of adverse events

This is provided in the Schedule of Assessments. Radiographic imaging is completed at the discretion of the investigator based upon the subject's condition and standard of care. If performed, the imaging should be sent to the core lab.

7.11. Retreatment

At the discretion of the investigator, a subject who has received a PulseRider device may be retreated (e.g. with coils, stent, etc.) at any time. All subjects who are retreated will remain in the study and will continue to receive all follow-up assessments based on the date of the index procedure per the Schedule of Assessments in Section 7.15. When a subject returns for a retreatment, this is considered an unscheduled visit and the evaluations noted for unscheduled visits must be completed. Data from the retreatment procedure will be captured in the appropriate eCRF, and data from the remaining unscheduled assessments will also be captured in the eCRFs. No pre-planned staged procedures on target aneurysms will be allowed in the study.

7.12. Early Termination

The study can be discontinued at the discretion of the investigator or study Sponsor for reasons including, but not limited to, the following:

- Per recommendation of the Data Monitoring Committee (DMC)
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Persistent non-compliance of a site with the protocol, or IRB/regulatory requirements

If the study is discontinued or suspended prematurely at a single clinical site (e.g. due to non-compliance or lack of enrollment), the Sponsor shall inform the clinical investigator/investigational center of the termination or suspension in enrollment and the reason for this. The Sponsor will also inform site personnel that although enrollment will be halted, the currently enrolled subjects will continue to be followed per protocol through

the five-year follow-up visit and then exited from the study. The Sponsor's communication to the investigator/investigational center will also include instructions for the investigator to promptly inform the IRB regarding the change in study status, along with the reason for termination or suspension by the Sponsor. Regulatory authorities may also need to be informed if deemed necessary.

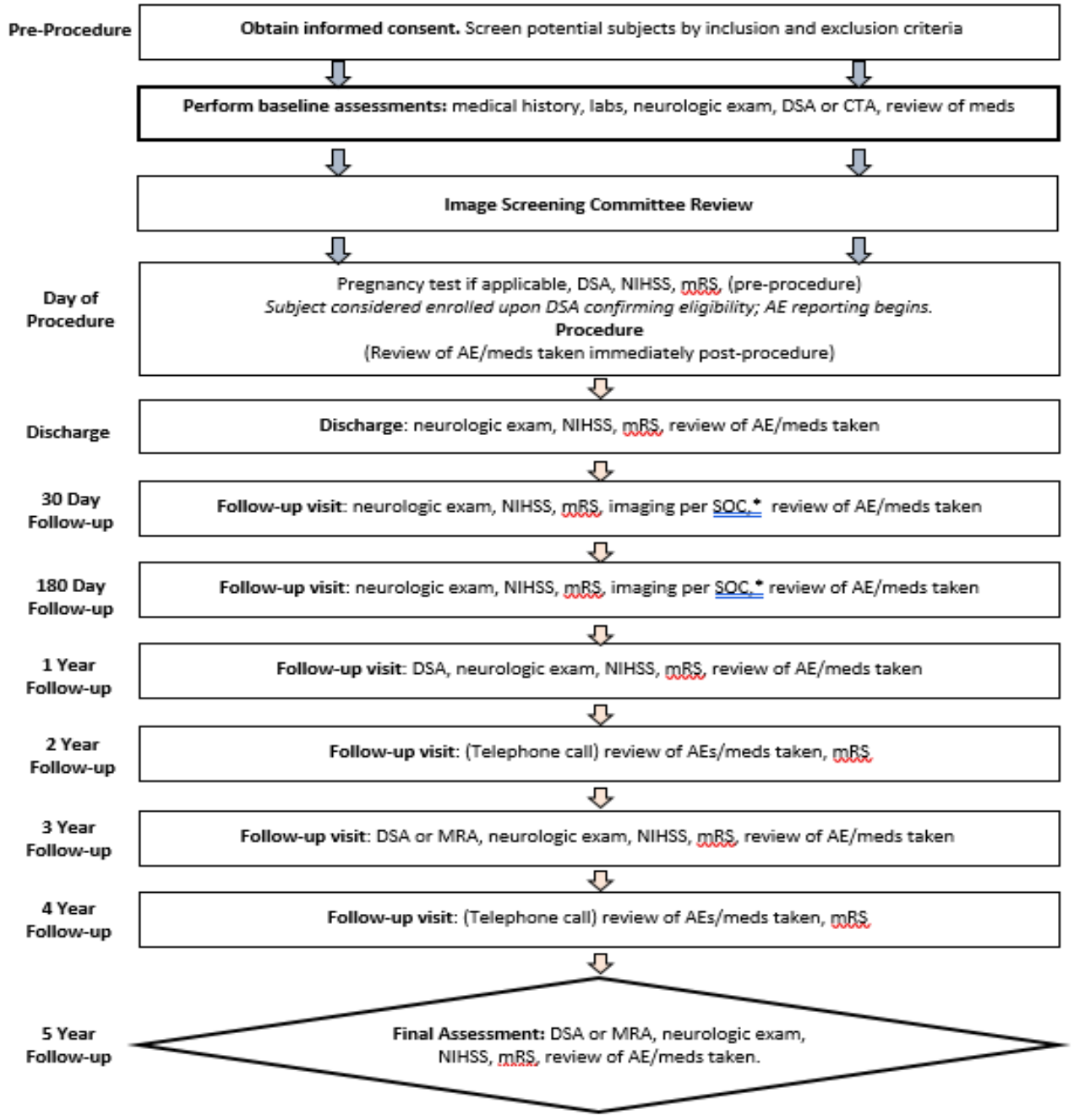
If the entire study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigators/investigational centers of the termination or suspension in enrollment and the reason for this. The Sponsor will also inform site personnel that although enrollment will be halted, the currently enrolled subjects will continue to be followed per protocol until one year visit for safety. Once the subject has completed the one year follow-up visit for safety, they will be exited from the study. The Sponsor's communication to the investigators/investigational centers will also include instructions for the investigator or their delegated study staff to promptly inform all consented subjects at their center, as well as the IRB regarding the change in study status along with the reason for termination or suspension by the Sponsor or by the clinical investigator. The Sponsor will notify the FDA in writing of the action, per regulations. Regulatory authorities and the personal physicians of the subjects may also need to be informed if deemed necessary.

7.13. Lost to Follow-up

Every attempt will be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up until the last study visit and unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information will include three attempts to make contact via telephone/email and if unsuccessful, then a letter from the investigator, sent via FedEx or similar traceable method, will be sent to the subject's last known address. Both contact logs and letter contact efforts to obtain follow-up will be recorded in the subject study files.

7.14. Schematic of Study Design

Figure 7.14A Schematic of Study Design



*All imaging performed per standard of care (SOC) after the study procedure and prior to the final visit will be submitted to the core lab.

7.15. Schedule of Assessments Table

This table provides an overview of the procedures to be performed at each study visit and the visit window.

Table 7.15A Schedule of Assessments

Assessments	Pre-procedure* (0-60 days of the procedure)	Immediately Pre-Procedure	Procedure	Immediately Post-procedure	Discharge	30 Day Follow-up (+/- 7 days)	180 Day Follow-up (+/-42 days)	1 Year Follow-up (+/-60 days)	2 Year Telephone Call (+/-60 days)	3 Year Follow-up (+/-60 days)	4 Year Telephone Call (+/-60 days)	5 Year Follow-up (+/-60 days)	Unscheduled Visit
Informed Consent	**X**												
Medical History	**X**												
Labs (CBC & Blood Coagulation Tests)	**X**												
Neurological Exam	**X**				**X**	**X**	**X**	**X**		**X**		**X**	**X**
NIH Stroke Scale Assessment		**X**			**X**	**X**	**X**	**X**		**X**		**X**	**X**
Modified Rankin Scale		**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Pregnancy Test		**X**‡											
Conventional Catheter Angiography – DSA$	****X**	*****X**				**O**β	**O**β	**X**†$	**O**β	**X**††	**O**β	**X**††	**O**β
MR Angiography$						**O**β	**O**β		**O**β	**X**††	**O**β	**X**††	**O**β
CT Angiography$	****X**					**O**β	**O**β		**O**β		**O**β		**O**β
Review of Adverse Events			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Review of Medications Taken	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Medical Resource HECON		X	X	X	X	X	X	X	X	X	X	X	X

*With the exception of the baseline DSA or CTA and the pregnancy test, all baseline evaluations must be completed within 60 days prior to the index procedure and may occur on the procedure day prior to the procedure.

**Baseline imaging may be either CTA or DSA and must be completed within 180 days prior to the index procedure.

***Three treatment angiograms: 1) Immediately pre-procedure image is before PulseRider implant to confirm eligibility 2) Procedure image immediately after PulseRider placement 3) Immediately post-procedure is after coiling.

β Any imaging related to the target aneurysm conducted post-procedure and prior to the final study visit, per standard of care, will be collected.

† Imaging for 1 year post-procedure must be DSA.

†† Imaging for 3 year 5 years post-procedure must be DSA or MRA.

‡ Pregnancy test must be completed on day of procedure for women of childbearing potential.

$ Subjects who were not implanted with the PulseRider device are not required to undergo DSA imaging at 1 year.

8. Assessment of Safety

8.1. Specific Safety Parameters

8.1.1. Adverse Event (AE)

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 14155:2011E).

- 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 the investigational medical devices

  For the purposes of this protocol, adverse events will be reported and recorded (via eCRF) if any of the following apply:

- The event is neurological in nature
- The event is a serious adverse event
- Causality is related to:
  - the device
  - the procedure
  - dual antiplatelet medication
  - if causality is unknown

Any medical condition that is present at the time the participant is screened or prior to the start of the study procedure will be considered as baseline and not reported as an AE. Such conditions should be added to medical history, if not previously reported.

8.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined (ISO 14155:2011E) as an adverse event that:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or

- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

- Led to fetal distress, fetal death or a congenital abnormality or birth defect

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.

8.1.3. Adverse Device Effect (ADE)

An adverse device effect is defined as an adverse event related to the use of an investigational medical device (ISO 14155:2011E).

- 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

8.1.4. Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of an SAE (ISO 14155:2011E).

8.1.5. Unanticipated Serious Adverse Device Effect (USADE)

Per ISO 14155:2011E, an unanticipated serious adverse device effect is 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.

- 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

8.1.6. Unanticipated Adverse Device Effect (UADE)

Per 21 CFR 812.3(s), an unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.7. Device Deficiency, Device Malfunction, and Use Error

All study device deficiencies shall be documented in the eCRF throughout the clinical investigation and appropriately managed by the Sponsor. If a study device deficiency is detected or suspected that could have led to a SADE, it should be documented on the appropriate eCRF, and the device failure and AE (if applicable) must be reported to the Sponsor within 72 hours upon study site staff awareness. All non-study device malfunctions should be reported via the manufacturer's complaints handling process.

A **device deficiency** is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

- Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device malfunction is defined as a 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 investigation plan.

Use error is defined as the act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

- Note 1: Use error includes slips, lapses, and mistakes.
- Note 2: An unexpected physiological response of the subject does not in itself constitute a use error

(ISO 14155:2011E)

8.2. Classification of an Adverse Event

8.2.1. Severity of Event

The intensity or severity of each AE must be assessed according to the following classifications:

Table 8.2.1A Intensity or Severity Definitions

Mild	Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

8.2.2. Relationship to Study Device and/or Procedure

The clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. Refer to Sections 8.5 and 8.6 regarding CEC and DMC interactions respectively.

Table 8.2.2A Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Causal relationship	The event is associated with the investigational device beyond reasonable doubt
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely
	Unlikely	The relationship with the use of the investigational device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
	Not related	Relationship to the investigational device can be excluded
Study Procedure	Causal relationship	The event is associated with the study procedure beyond reasonable doubt
	Probable	The relationship with the study procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possible	The relationship with the study procedure is weak but cannot be ruled out completely
	Unlikely	The relationship with the study procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
	Not related	Relationship to the procedure can be excluded

8.2.3. Outcome

The outcome of each AE must be assessed according to the following classifications:

Table 8.2.3A Adverse Event Outcome Classifications

Classification		Definition
Recovered/Resolved		Subject fully recovered with no observable residual effects
Recovered/Resolved with sequelae		Subject recovered with observable residual effects
Recovering/Resolving	**Improved**	Subject's condition improved, but residual effects remain
	Unchanged	AE is ongoing without changes in the overall condition
	Worsened	Subject's overall condition worsened
Fatal		Subject died as a result of the AE (whether or not the AE is related to the device or procedure)

8.3. Time Period and Frequency for Adverse Event Assessment and Follow-up

Adverse events shall be assessed and documented starting at the point the subject is considered enrolled (after the patient is consented, imaging screening committee approval is received, pre-procedure angiogram is completed and the treating physician confirms the subject meets all eligibility criteria) and at all study follow-up visits. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events. Adverse events that occur during this study should be treated by established standards of care which will protect the life and safety of the subject. Events will be followed for outcome information until resolution, stabilization or the subject exits the study, whichever occurs first. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

8.4. Reporting Procedures

8.4.1. Adverse Event Documentation and Reporting Requirements

Reportable adverse events will be recorded and reported on the eCRFs throughout the study and provided to the Sponsor. (In the event EDC is unavailable, adverse events can be notified via email to the NAPA IDE study mailbox: RA-BWIUS-PulseRider@ITS.JNJ.com. Note: the adverse event(s) will still need to be recorded on eCRFs once EDC is functional.)

- If an adverse event occurs, all sections of the Adverse Event eCRF must be completed
- In the case of serious device effects and device deficiencies that could have led to serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

- Copies of all relevant source documentation (i.e. procedure reports, physician/nursing notes, discharge summary, etc.) should be compiled and provided to the Sponsor for the adjudication process for all AEs recorded in the study.

Timing for reporting the different types of AEs and Device Deficiencies is described in Table 8.4.1A.

Table 8.4.1A Adverse Event Reporting Requirements

Type of Adverse Event	Reporting Requirements
• SAE • SADE • USADE • Death • Any study device malfunctions that could have led to an SADE*	Report to Sponsor immediately upon study site staff awareness of event but no later than 72 hours
UADE	Report to Sponsor immediately upon study site staff awareness of event but no later than 72 hours, followed by a written report within 10 working days after investigator first learns of the effect to Sponsor and IRB
• All other adverse events • All other study device malfunctions*	Report to Sponsor immediately upon study site staff awareness but no later than 14 calendar days

* Non-study device malfunctions should be reported via the manufacturer's complaints handling process.

The Investigator will report all of the above to the reviewing IRB according to the local reporting requirements.

8.4.2. Serious Adverse Event Reporting

All SAEs, whether or not they are related to the device or procedure, must be reported to the Sponsor, via eCRF, **immediately upon study site staff awareness of event but no later than 72 hours** by the study site personnel. (In the event EDC is unavailable, adverse events can be notified via email to the NAPA IDE study mailbox: RA-BWIUS-PulseRider@ITS.JNJ.com. Note: the adverse event(s) will still need to be recorded on eCRFs once EDC is functional.)

The study investigator shall report the SAE to the reviewing IRB in accordance with the local IRB requirements.

8.4.3. Unanticipated Adverse Device Effect Reporting

All UADE/SADE/USADEs must be reported to the Sponsor, via eCRF, **immediately upon study site staff awareness of the event but no later than 72 hours after study site staff awareness of the event**. (In the event EDC is unavailable, adverse events can be notified via email to the NAPA IDE study mailbox: RA-BWIUS-PulseRider@ITS.JNJ.com. Note: the adverse event(s) will still need to be recorded on eCRFs once EDC is functional.) An investigator shall submit to the reviewing IRB and the Sponsor a written report of any unanticipated adverse device effect occurring during an investigation no later than 10 working days after the investigator first learns of the effect.

Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the Sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1).

A Sponsor who determines that a UADE presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect. 21 CFR 812.46(b(2).

8.5. Clinical Events Committee

The Clinical Events Committee (CEC) will consist of a minimum of three independent physicians with expertise in neurosurgery, neurology or interventional neuroradiology and who are not otherwise involved with the study. The CEC will review all reportable adverse events to adjudicate the safety endpoint, in addition to AEs of interest specified in the CEC charter.

8.6. Data Monitoring Committee

An Independent DMC will be responsible for assessing all reported AEs and monitoring the accumulated interim data on a periodic basis as the study progresses to ensure subject safety. The DMC will be comprised of representatives from multiple disciplines including but not limited to neurosurgery, neurology, interventional neuroradiology and biostatistics. The DMC will advise the Sponsor regarding the continuing safety of subjects and those yet to be recruited to the study, as well as the continuing validity and scientific merit of the study. The DMC will provide recommendations to the Sponsor regarding stopping or continuing enrollment in the study. The DMC will operate according to an approved charter.

9. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that study data are accurate, complete, and verifiable, and that study conduct is in compliance with 21 CFR 812 and 50, ISO 14155, the currently approved protocol, with Good Clinical Practices, and with applicable regulatory requirements. Each site will undergo periodic monitoring visits, and subject medical records shall be made available during the visits.

Monitoring visits may include but are not limited to the following:

- Protocol adherence
- Source documentation verification and accuracy of the eCRFs
- Verification that informed consent is being obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the Regulatory Binder
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, Device Accountability, etc.
- Compliance with applicable regulations
- Identification and action to resolve any issues or problems with the study.

Data are to be submitted promptly via eCRF after collection. Missing or unclear data will be queried to be corrected as necessary throughout the study. Pulsar Vascular, Inc. will request further documentation such as physician notes, outside hospital records, etc. when further documentation is required to understand any adverse events. Monitoring will be conducted in accordance with the monitoring plan.

10. Statistical Methodology

The following sections provide a general description of the statistical plan for the analysis of study data. A separate Statistical Analysis Plan (SAP) document that provides greater detail on data derivations and the analyses to be performed will be developed and approved prior to the first DMC data analysis report. The SAP will reflect the protocol and any amendments that have been implemented at the time the SAP is finalized. Any deviations from the final SAP will be noted in the final clinical summary report.

10.1. Primary and Secondary Endpoints, and Associated Hypotheses

10.1.1. Primary Endpoints and Associated Hypotheses

The primary safety endpoint is the composite of Neurological Death or Major Ipsilateral Stroke (in downstream territory) up to 1 year post-procedure. The primary effectiveness endpoint is the rate of complete aneurysm occlusion (Raymond I) without significant parent artery stenosis (> 50% stenosis) or re-treatment at 1 year post-procedure.

To establish performance goals for safety and effectiveness for the treatment of wide neck bifurcation aneurysms (WNBAs), Fiorella et al. conducted a meta-analysis of literature published from 2000 via PubMed. A complete description of the systematic literature review and analysis can be found in the article. In summary, articles were identified using predetermined search terms and subsequently screened for inclusion/exclusion resulting in 43 unique references and 53 unique articles for effectiveness and safety, respectively. Sub-group analyses by aneurysm location (anterior vs. posterior) and treatment modality (surgical clipping (SC) and endovascular treatment (EVT) was also performed. A composite safety endpoint of major adverse events was applied with effectiveness outcomes reported as complete occlusion (Raymond I) and adequate occlusion (Raymond I and II) with at least one follow-up image at 12 months (range 4-25 months) post procedure. Notably, a 12% adjustment for non-core laboratory adjudicated images was made. The authors reported adequate occlusion rates for all therapies as 59.4% and 43.8% and 69.7% for EVT and SC, respectively. The rates of occurrence for pre-specified safety endpoints were 18.7% combined, and 21.1% and 24.3 % for EVT, and SC, respectively.

Considering the similarities in the NAPA IDE target subject population and primary effectiveness endpoint (complete occlusion at 1 year post-procedure) to that which was evaluated in Fiorella et. al., the incidence of 46.3 % reported in the meta-analysis was used to generate a proposed NAPA IDE performance goal for effectiveness of 46.3%. Based on the experience with the ANSWER study which evaluated the PulseRider device, the rate of adequate occlusion with the PulseRider device is expected to be at least 58.8%.

The composite safety endpoint applied by Fiorella et al. is reasonably dissimilar to the NAPA IDE primary safety endpoint of major ipsilateral stroke or death due to neurological causes at 1 year post-procedure. As a result, the NAPA IDE performance goals for safety was determined from a systematic review of literature published in OVID and PubMed between January 1, 2012 and April 25, 2017. After de-duplication, a full text search in QUOSA was performed limiting results to WNBA located at NAPA IDE aneurysm locations. The following inclusion/ criteria were applied, yielding 7 unique articles for safety with Forest Plot shown in Figure 10.1.1A. [Brassel 2015, Fields 2011, Labeyrie 2017, Pierot 2015, Peirot 2015 Sivan-Hoffman 2015, Zhao 2012].

Included articles:

- Article reporting clinical performance and safety results on equivalent comparator(s) [WEB, pCONUS, BARREL, X/Y stenting]
- Wide neck or complex bifurcation aneurysms found at MCA, ACOM, Basilar tip, carotid terminus with at least 80% or more unruptured aneurysms and where $\geq$ 5 patients were included in a series
- Clinical follow-up between 10 and 14 months;

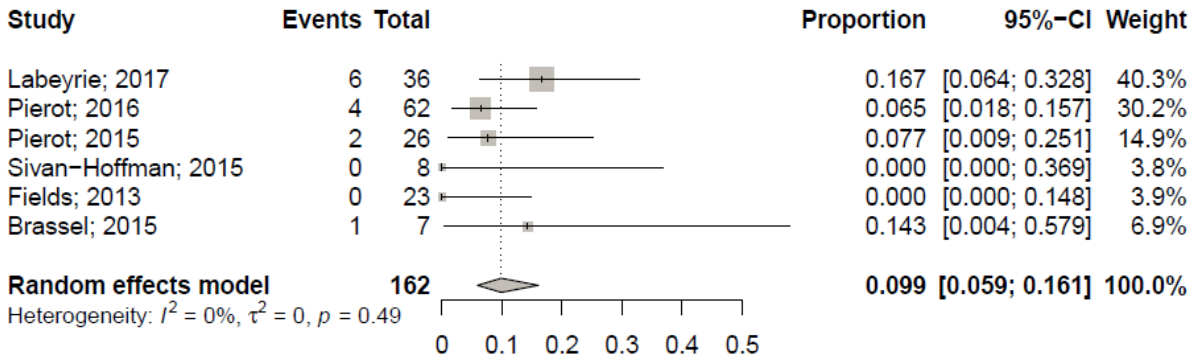
Excluded articles:

- Technical or reviews (systematic and none) with non-extractable data by treatment modality

- No clinical performance and safety results on target device(s) and/or equivalent comparator(s)
- Use of the target device(s) and/or equivalent comparator(s) was not the main focus of the study
- Studies where the subject device was used in patients, but no safety or performance outcomes were reported
- Abstract, report, or article could not be retrieved
- Duplicate or non-English articles language

Of the included articles, all reported safety events were evaluated and neurological deficits that resulted in a sudden change in NIHSS of 4 or more (when reported) or as determined by a Codman neurosurgeon to cause a change in NIHHS of 4 or more were deemed to meet the primary safety endpoint. Based on this meta-analysis, a rate of 9.9% rounded to 10% (95% CI: 5.9% - 16.1%) for death due to neurological causes or major ipsilateral stroke was identified. A 5% margin of indifference for the primary safety endpoint is proposed, resulting in a Performance Goal (PG) of 15% for this endpoint.

Figure 10.1.1A Forest Plot: Seven References with Usable Data to Estimate the Anticipated Primary Safety Endpoint at 12 Months



Primary Safety Endpoint Hypotheses:

Null Hypothesis H_0: $p_{\text{Major Stroke/Death}} \geq 15\%$

Alternative hypothesis H_A: $p_{\text{Major Stroke/Death}} < 15\%$

Where $p_{\text{Major Stroke/Death}}$ is the rate of Composite of Neurological Death or Major Ipsilateral Stroke (in downstream territory) up to 1 year post-procedure.

Decision Criterion: The decision will be made to reject the null hypotheses and conclude the alternative hypothesis if the upper bound of a two-sided 95% normal approximation based confidence interval is < 15%.

Primary Effectiveness Endpoint Hypotheses:

Null hypothesis H_0: $p_{CompleteOcclusion} \leq 46.34\%$

Alternative hypothesis H_A: $p_{CompleteOcclusion} > 46.3\%$

Where $p_{CompleteOcclusion}$ is the rate of complete aneurysm occlusion without significant parent artery stenosis (> 50% stenosis) or prior retreatment at 1 year post-procedure.

Decision Criterion: The decision will be made to reject the null hypotheses and conclude the alternative hypothesis if the lower bound of a two-sided 95% normal approximation based confidence interval is > 46.3%.

Study Success:

The study will be deemed to be a success if the primary safety and effectiveness endpoint null hypotheses are both rejected.

10.1.2. Secondary Endpoints

- Technical Success is defined as successful implantation of device— physician able to access target aneurysm, deploy PulseRider device at the neck of aneurysm and device was detached successfully. This endpoint will be reported by the investigator. The following hypothesis test of this endpoint will be performed if the primary safety and effectiveness endpoint null hypotheses are both rejected:
  - Null hypothesis H0: pTechnicalSuccess ≤ PG of 79%
  - Alternative hypothesis HA: pTechnicalSuccess > PG of 79%
  - Where pTechnicalSuccess is the rate of technical success
  - Decision Criterion: The decision will be made to reject the null hypotheses and conclude the alternative hypothesis if the lower bound of a two-sided 95% normal approximation based confidence interval is > PG of 79%. With 160 subjects, a rate for technical success of at least 85% is required to demonstrate success on this endpoint.
- Ability to retain embolic coils within aneurysm immediately post-procedure (as evaluated by the core lab)
- Complete aneurysm occlusion at 3 years and 5 years. Complete aneurysm occlusion is defined as Raymond I. Aneurysm occlusion grading will be evaluated by the independent core laboratory.
- Adequate aneurysm occlusion (defined as Raymond I and II combined) at 1 year, 3 years and at 5 years. Aneurysm occlusion grading will be evaluated by the independent core laboratory.
- The percentage of target aneurysms that are retreated through 1 year, 3 years and 5 years. Retreatment will be reported by the investigator.

- The percentage of subjects with significant stenosis defined as > 50% at implant site at 1 year, 3 years and 5 years. This endpoint will be evaluated by the independent core laboratory
- The percentage of subjects with mRS 0 – 2 at 1 year, 3 years and 5 years

10.1.3. Additional Endpoints

- The percentage of target aneurysm ruptures up to 1 year, 3 years and 5 years. This endpoint will be evaluated by the independent core laboratory.
- No migration (defined as ≤ 2 mm) of the device at 1 year, 3 years and 5 years. This endpoint will be evaluated by the independent core laboratory.

10.1.4. Adverse Events and Clinical Complications

Adverse Events, SAEs, device- or procedure-related AEs, USADEs, UADEs, and deaths will be coded using the MedDRA system and summarized with frequencies.

Study device malfunctions will also be summarized.

In addition, a listing of adverse events will be provided for any subject that was consented and started the study procedure but did not undergo attempted treatment with the study device and therefore is not part of the modified Intent To Treat (mITT) population.

10.1.5. Levels of Significance

A 2-sided alpha of 0.05 will be used for statistical testing and confidence intervals unless otherwise noted. There will be no adjustment of significance levels or p-values for testing multiple hypotheses Both primary endpoints must be met for study success and the secondary effectiveness endpoint of technical success will only be tested if the primary endpoints are met.

10.1.6. Analysis Datasets

Modified Intent to Treat Analysis Set

The mITT analysis set consists of all enrolled subjects in whom treatment with the PulseRider device is attempted as defined by advancement of any portion of the PulseRider device outside of the distal end of the microcatheter inside the subject. This includes subjects in which the PulseRider is not fully advanced outside of the microcatheter. It is possible that the PulseRider device may not reach the target aneurysm, and as a result the treating physician does not advance the device outside of the distal end of the microcatheter. In the rare event that this happens, the subject will not be considered part of the mITT population and will instead be followed for 30 days.

Per Protocol (PP) Analysis Set

The PP analysis set consists of all subjects who meet the following criteria:

- there are no major deviations from the protocol eligibility criteria or DAPT requirements
- the subject is successfully implanted with the PulseRider device

10.2. Sample Size Justification

Meta-analysis

As described above, a meta-analysis was executed to determine the safety Performance Goals for the proposed NAPA clinical study of the PulseRider using the R package 'meta[a]' in a [R] environment, version 3.3-2. To obtain an overall proportion from studies reporting a single proportion, a random-effects model was chosen over a fixed-effect model to acknowledge the variations in study design. Additional characteristics of the methodology are:

- Inverse variance method used for weights
- DerSimonian-Laird method used to estimate tau^2
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies

Based on this meta-analysis, a rate of 9.9% rounded to 10% (95% CI: 5.9% - 16.1%) for death due to neurological causes or major ipsilateral stroke was calculated. A 5% margin of indifference for the primary safety endpoint is proposed, resulting in a PG of 15% for this endpoint. Based on the 1 year results of the ANSWER HDE Study, the anticipated rate for the primary safety endpoint is 7%. Results from a recently published meta-analysis [Fiorella 2017] of wide-neck bifurcation aneurysms indicate that the rate of complete occlusion at 1 year of wide-neck bifurcated aneurysms treated with conventional therapies is 46.3% (95% CI: 39.2% - 53.4%) whereas based on the ANSWER HDE Study the rate of complete occlusion is expected to be 58.8% with the PulseRider device. With Sponsor's desire to seek superiority to a PG of 46.3% for the primary effectiveness endpoint and an expected attrition rate of 10%, one hundred sixty (160) subjects will provide 80% power for the primary safety endpoint and 85% power for the primary effectiveness endpoint.

10.3. Analyses to be Conducted

10.3.1. General Conventions

Standard descriptive summaries for continuous data include the number of observations with data, number of observations with missing data, mean, standard deviation, median, minimum, and maximum values. For categorical data, the count and percent will be provided. Percentages will be based on the number of subjects without missing data.

Analyses will take place using SAS statistical software version 9.4 or later in a server environment.

[a] Schwarzer G. Package 'meta'. *Meta-analysis with R*, Version 4.7-0. 2015

10.3.2. Disposition of Study Subjects

Subject disposition will be summarized in multiple ways:

- With a summary of the number of subjects enrolled and treated by site/investigator
- With a subject flow diagram which shows the number of enrolled, discontinued, lost to follow-up, withdrawn/early terminated, and completed subjects
- With a subject accounting table

10.3.3. Demographics, Baseline, and Procedural Characteristics

All demographic characteristics, procedural, and immediate post-operative details will be summarized using the mITT analysis set, including but not limited to: age, sex, medical history, smoking status, prior treatment, aneurysm location, neck and diameter size, pre and post procedural DAPT, length of procedure, and length of hospital stay.

10.3.4. Primary Endpoint Analyses

Primary Safety Endpoint

The primary safety endpoint analysis will be conducted on the mITT analysis set.

If a subject experienced a death due to neurological causes or a major ipsilateral stroke in downstream territory within a year post-procedure then subject will be deemed a failure on the endpoint. If a subject completed the 1 year follow up and did not experience any such event then subject will be deemed a success on the endpoint. If a subject did not complete the 1 year follow up and did not experience such event then the subject will be imputed with a multiple imputation method that will make use of the similarities between the subject's demographic, procedural, and aneurysm characteristics with those of the subjects with a non-missing endpoint (those who either experienced an event and those who completed the study without experiencing an event). The imputation method will also account for the length of time between the procedure and the last time the subject was seen. The longer that time period is, the less likely the subject will be imputed with an event.

Subjects for whom implantation of the PulseRider was attempted but not successful will be followed up to a year. Any safety events which occur due to attempted implant or from retreatment, and which meet the primary safety endpoint definition will count as failures in the analysis. If such a subject is lost to follow-up then subject will be imputed with data based on other subjects for whom the implantation was not successful but who were not lost to follow-up.

The multiple imputation method results in a large collection of imputed datasets. The proportion of primary endpoint events and its variance is computed for each dataset. Within and between imputation variances are then combined according to Rubin's method [Rubin 1996] in order to produce a single variance estimate for the proportion of events.

The endpoint will be considered successful if the upper bound of the 2-sided 95% normal approximation based confidence interval for the rate of events is less than a performance goal of 15%.

Primary Effectiveness Endpoint

The primary effectiveness endpoint analysis will be conducted on the PP analysis set.

Success on this endpoint is defined as complete aneurysm occlusion (Raymond I) without retreatment or significant parent artery stenosis (> 50% stenosis) at 1 year post-procedure. If the 1 year imaging is not available and if the subject did not experience a retreatment then the subject will be imputed using an imputation method that will make use of the subject's own past occlusion and stenosis evaluations if available and the similarities between the subject's demographic, procedural, and aneurysm characteristics with those of the subjects with a non-missing endpoint.

The multiple imputation method results in a large collection of imputed datasets. The proportion of complete aneurysm occlusion and its variance is computed for each dataset. Within and between imputation variances are then combined according to Rubin's method in order to produce a single variance estimate for the proportion of complete aneurysm occlusion.

The endpoint will be considered successful if the lower bound of the 2-sided 95% normal approximation based confidence interval for the rate is greater than a performance goal of 46.3%.

10.3.5. Secondary Endpoint Analyses

The analysis of technical success which is reported by the investigator will be conducted on the mITT analysis set. The endpoint will be considered successful if the lower bound of the 2-sided 95% normal approximation based confidence interval for the rate is greater than a performance goal of 79%.

The analyses of the remaining secondary effectiveness endpoints listed below will be conducted on the PP analysis set using the observed data.

- The ability to retain embolic coils within aneurysm immediately post-procedure as reported by the independent core laboratory
- Complete aneurysm occlusion at 3 years and 5 years as reported by the independent core laboratory
- Adequate aneurysm occlusion at 1 year, at 3 years and 5 years as reported by the independent core laboratory
- The percentage of target aneurysms that are retreated through the 1 year, 3 year and 5 year as reported by the investigator
- The percentage of subjects with significant stenosis defined as > 50% at implant site at 1 year, 3 years and 5 years as reported by the independent core laboratory
- The percentage of subjects with mRS 0-2 at 1 year, 3 years and 5 years

10.3.6. Additional Endpoint Analyses

The analyses of the percentage of target aneurysm ruptures up to 1 year, 3 years and 5 years post-procedure and of the percentage of no migration (defined as ≤ 2 mm) of the device at 1 year, 3 years and 5 years post-procedure will be conducted on the PP population using the observed data. Both endpoints are evaluated by the independent core laboratory.

10.3.7. Safety Analyses

AE summaries (number of events and incidence) conducted on the mITT analysis set will be presented for:

- All AEs
- SAEs
- UADEs
- Deaths
- Device and Procedure Related AEs
- Neurologic AEs

Study device malfunctions observed intra-operatively and overtime thereafter will be summarized using the mITT analysis set.

AE and study device malfunction summaries will also be provided in the same fashion as above for T and Y shape devices separately.

10.3.8. Plans for Interim Analyses

There are no planned interim analyses.

10.3.9. Handling of Missing Data

Missing primary safety and effectiveness endpoint data will be imputed as per the multiple imputation method described in section 10.3.4. The secondary effectiveness endpoint is expected to have minimal to no missing data and analysis will not make use of any imputations.

10.3.10. Sensitivity Analyses

As a sensitivity analysis, the primary safety and effectiveness endpoints will be analyzed as described in section 10.5.4 but without imputing missing endpoint data using the Clopper-Pearson method.

Other sensitivity analyses will analyze the primary endpoints as follows:

- Consider all missing endpoints as successes,
- Consider all missing endpoints as failures,
- A Tipping point analysis which attempts to answer how many subjects with missing primary endpoint data need to change to either successes or failures for success on the endpoint to no longer hold.

10.3.11. Sub-Group Analyses

Proportions of subjects and 95% confidence intervals of the primary safety and effectiveness endpoints will be presented for the mITT population set with only the observed data and of the primary effectiveness endpoint for the PP population set with only the observed data as appropriate, in the following subgroups:

- sex. Males and Females will also be statistically compared at the 0.1 alpha level using a chi-square test based on a normal distribution.
- race
- ethnicity
- age category (18-35, 36-50, 51-64, 65-75, and 76-80 years)
- aneurysm location - basilar, carotid terminus, MCA and ACOM

10.3.12. Assessment of Site Homogeneity

Homogeneity of the primary safety and effectiveness endpoints across sites will be assessed with a chi-square test of proportions at an alpha level of 0.1 and will be conducted on the mITT population set for the safety endpoint and on the PP population set for the effectiveness endpoints using the observed data only for both. Sites with less than 5 subjects will be pooled.

10.4. Measures to Minimize Bias

Pulsar Vascular, Inc. will be diligent in controlling for bias by utilizing proper study design and implementation of the approved study protocol. IRB approval will be obtained at all clinical sites prior to study initiation. Study agreements/contracts will be made with the hospitals/universities and all compensation for conduct of the study will be paid to the hospitals/universities and not to the investigators. Strict inclusion and exclusion criteria will be implemented to avoid selection bias.

Investigators will assess potential subjects who are candidates for the study. In addition, an image of the subject's aneurysm and branch arteries must be reviewed and approved by the Image Screening Committee. Candidates who meet the protocol inclusion/exclusion criteria with at least one bifurcation intracranial aneurysm that is acceptable for minimally invasive treatment and approved by the Image Screening Committee may be enrolled.

A Clinical Events Committee (CEC) will review all reportable adverse events and adjudicate endpoints to determine whether they meet protocol-specified criteria. The CEC will review all reportable adverse events to adjudicate the safety endpoint, in addition to AEs of interest specified in the CEC charter. CEC members will provide an impartial review and will not hold a financial interest in Pulsar Vascular, Inc. An independent core laboratory will perform the angiographic assessments for the primary and secondary effectiveness endpoints. These evaluations will be performed by an independent reader who does not hold a financial interest in Pulsar Vascular, Inc.

Clinical outcomes will be measured in a standardized manner using the National Institutes of Health Stroke Scale, a standardized, objective, clinical assessment tool used to quantify and document the neurological status of patients and to act as a predictor for clinical outcomes. It is used to determine stroke and the severity of stroke.

Clinical outcomes will be measured in a standardized manner using the Modified Rankin Scale , a commonly utilized six-point scale measuring functional outcome and disability in patients with stroke. The mRS measures independence and dependence related to activities of daily living and can be used over time to determine recovery or regression.

Study monitors will have clinical research experience and be proficient at study monitoring. Study data will be source data verified (SDV) using the subject's medical records, study source worksheets, clinic notes, and radiographic reports as applicable as source documentation.

11. Ethics and Protection of Human Subjects

11.1. Ethical Standard

As the Sponsor of this study, Pulsar Vascular, Inc. has the overall responsibility for the conduct of the study, including assurance that the study is in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as well as the regulatory requirements of the Food and Drug Administration and local government. The Sponsor will also maintain compliance with Good Clinical Practice (International Conference on Harmonization (ICH) version 4 du 1 May 1996), the European standard EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects), Sponsor general responsibilities (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]), maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b)]), and to local regulations where required.

- General Responsibilities

Sponsor's general duties consist of submitting the IDE application to FDA, assuring that sites have received IRB approvals prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained. Any additional requirements imposed by an IRB or regulatory authority shall be followed, if appropriate.

- Data Quality and Reporting

Sponsor is responsible for providing quality data that satisfy federal regulations and informing proper authorities of unanticipated adverse effects and deviations from the protocol.

- Selection of Investigators

Sponsor will select qualified investigators, obtain a signed Investigator Agreement and provide the investigators with the information necessary to conduct the study.

- Supplemental Applications—Protocol Amendments

As appropriate, Sponsor will submit changes in the study protocol to the FDA and investigators to obtain IRB re-approval. A justification for each amendment will be documented.

- Maintaining Records

Sponsor will maintain copies of correspondence, device shipment and disposition records, data, adverse device effects and other records related to the study. Sponsor will maintain records related to the signed Investigator Agreements and financial disclosure.

- Submitting Reports

Sponsor will submit any required regulatory reports identified in this section of the regulation. This includes unanticipated adverse device effects, withdrawal of FDA approval, current investigators list, annual progress reports, recall information, final reports and device use without informed consent.

11.2. Institutional Review Board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. IRB approval of both the protocol and the consent form must be obtained before any participant is consented. A stamped copy of the IRB approval letter and approved consent form must be submitted to Pulsar Vascular, Inc. certifying study approval prior to subject consent.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. Pulsar Vascular, Inc. and the IRB must approve in writing any changes to the protocol that affect the rights safety and/or welfare of the subjects or may adversely affect the validity of the study. All changes to the consent form will be IRB approved and a determination will be made regarding whether previously consented participants need to be re-consented.

Investigators are responsible for submitting and obtaining initial and continuing review of the study by their IRB.

11.3. Informed Consent Process

11.3.1. Consent and Other Informational Documents Provided to Participants

Patient's informed consent must be obtained and documented according to the principles of informed consent in 21 CFR Part 50, the ethical principles that have their origin in the Declaration of Helsinki (Brazil, 2013), and ISO 14155:2011.

The IRB must review and approve an informed consent form (ICF) specific to this study. Pulsar Vascular, Inc. will provide each study center with an example ICF. The clinical center, to meet specific IRB requirements, may modify this example ICF; however, the ICF must contain all of the informed consent elements required by 21 CFR 50.25. Each investigational site will provide Pulsar Vascular, Inc. with a copy of the IRB approved ICF

and renewed approvals and consents as appropriate for the duration of the study. The original, signed and dated ICF should be retained by the investigational site for monitoring, and a copy provided to the subject.

11.3.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's study participation. Discussion of risks and possible benefits of participation will be discussed with the patients and their families as requested. The investigator, or designee, will explain the research study to the patient and answer any questions that may arise. All patients will receive verbal and written information in language at a level of complexity understandable to the patient about the purpose, procedures, and potential risks of the study and of their rights as research participants. Patients will have ample opportunity to review the written consent form and to ask questions prior to signing. The patients should be allowed additional time as desired to consider the study prior to agreeing to participate. Prior to participation in the study, the Patient Informed Consent Form will be signed and personally dated by the patient or his/her legal representative. The subjects may withdraw consent at any time throughout the course of the study. The rights and welfare of the participants will be protected and it will be emphasized to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A signed and dated copy of the Patient Informed Consent Form must be collected from each enrolled subject and kept in the study subject files. Subjects will be notified in a timely manner of any significant new information that develops over the course of the study that may affect their willingness to participate.

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) or as required per local regulations. Subject confidentiality will be maintained throughout the clinical study in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the study may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

It is not expected that the PulseRider device will be used emergently as eligibility confirmation includes a screening process, therefore, consent under emergency circumstances does not apply.

11.4. Participant and Data Confidentiality

During this clinical investigation, all representatives of the Sponsor will comply with all in-country privacy laws, including HIPAA and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Pulsar Vascular, Inc. concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized

Pulsar Vascular, Inc. personnel or representatives (including contracted service providers, i.e. Core Lab, Clinical Research Associate, etc.), representatives of the FDA will have access to these confidential files upon request (including, but not limited to, laboratory test result reports, admissions/discharge summaries for hospital admission occurring during a subject's study participation and autopsy reports for deaths occurring during the clinical investigation). All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

12. Quality Assurance and Quality Control

Quality Control (QC) procedures will be implemented beginning with the data entry system and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written (Standard Operating Procedures) SOPs, monitors will verify that the clinical study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements. If noncompliance is identified, Sponsor is required by regulation to implement measures to secure compliance.

The investigational site will provide direct access to all study related information, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

13. Data Handling and Record Keeping

13.1. Data Collection and Management Responsibility

Data collection is the responsibility of the site clinical study staff under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data entered. The Sponsor is responsible for all data management activities. These activities include the development of a database, utilizing validated database software, into which all study data will be entered by the clinical sites. The Sponsor will be responsible for ensuring the overall integrity of the database.

13.1.1. Electronic Case Report Forms

Electronic CRFs have been developed to capture the information outlined in this study protocol. Data on these eCRFs will be monitored, corrected if necessary, and entered into a validated database. All changes made to the data will be tracked in the electronic audit trail, recording the current value, previous value, reason for change, date timestamp of data entry/change, and the name of the person who changed the data. The investigator will electronically sign all subject eCRFs as verification that the data have been reviewed and correctly reflects source documentation. Data from these eCRFs will be used to provide analysis of this study.

13.1.2. Source Documentation

Data entered on to the eCRFs will be obtained from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or clinic document exists to capture information required specifically for this clinical investigation, a source worksheet may be developed to record this information. Any worksheets shall be signed by the investigator at the given site and will serve as the source document for those data parameters. These source documents will serve as the basis for monitoring subject specific information against the eCRFs.

Electronic subject records will be considered source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records will have to be printed and added to the subject's paper file. A print-out of an eCRF cannot be used as source documentation.

13.1.3. Study Records

Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the eCRFs. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain ***original*** source documents from which study-related data are derived, which include, but are not limited to:

- Clinic progress notes recording subject's medical history and medications
- Medical charts with operative reports and condition of subject upon discharge
- Medical records regarding AEs, including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging (such as x-rays, MRIs), as well as the report of the radiologist's reading/interpretation of diagnostic imaging
- Notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to subject death (e.g., death certificate, autopsy report)
- Print-outs of source data generated by technical equipment (e.g., x-rays, MRIs) must be filed with the subject's records.

Only authorized Pulsar Vascular, Inc. personnel or representatives, authorized site personnel, local government authorities, or the FDA, acting in their official capacities, will have access to these confidential files.

13.1.4. Health Economic Data

The cost and frequency of health care utilization during hospitalization for the study index procedure and any additional hospitalizations during the study period will be collected.

This data will not be provided to the FDA as part of the IDE reporting because it does not support the safety and efficacy of the investigational device.

The hospitalization health care data to be collected may include, but is not limited to, the subject's admission date, discharge date, procedure date, ICD-10 and procedure codes, DRG assignment and total cost for the hospitalization will be extracted from the information.

In addition, the Sponsor will collect health economic data associated with follow up care including any additional or necessary procedures/surgeries resulting from the index procedure, ER visits, and/or outpatient visits to address issues related to the target intracranial aneurysm. Data collected may include quality of life data, additional procedures data, any devices utilized, length of hospital stay, readmissions, procedure time, and hospital charges.

13.1.5. Data Reporting

The investigator, or designated individual, is responsible for timely completion of all data from the study via the eCRFs supplied by Pulsar Vascular, Inc. The investigator/delegated individual is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed, and attests to the correctness, of the recorded data. Completed eCRFs will be reviewed and monitored at the investigational site by Pulsar Vascular, Inc. personnel or designee at regular intervals throughout the study. To this end, the investigator and institution must permit inspection of the study files and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the IRB and Pulsar Vascular, Inc., as applicable.

13.1.6. Data Verification and Review

Pulsar Vascular, Inc. will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments. Missing or unclear data will be queried as necessary throughout the study. Pulsar Vascular, Inc. will request further documentation such as physician and/or radiology reports when complications or malfunctions are observed and reported. Pulsar Vascular, Inc. will be responsible for auditing the database and confirming the overall integrity of the data.

13.1.7. Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

13.2. Study Record Retention and Archiving

The investigator will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with FDA guidelines per 21

CFR 812.140(d). Documents must be retained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. Pulsar Vascular, Inc. must receive written notification of this custodial change.

14. Protocol Deviations

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures described in the protocol, FDA regulations and any conditions required by the reviewing IRB. A protocol deviation is a failure to comply (intentionally or unintentionally) with the requirements of the clinical study as specified in the protocol. Examples of protocol deviations include late visits, missed visits, required follow-up testing not completed, visit out of window, non-adherence to inclusion/exclusion criteria, etc. and shall be reported to the Sponsor through the eCRFs. Deviations will be reviewed and assessed by the Sponsor.

It is the responsibility of the site to use vigilance to identify and report deviations to the Sponsor and IRB per guidelines. The study monitors shall verify that the conduct of the study is in compliance with the approved protocol and applicable regulations and shall identify deviations and any issues of noncompliance. Corrective and preventative actions will be implemented promptly as necessary and significant protocol deviations that raise subject safety concerns or indicate repeat noncompliance may be grounds for investigator disqualification.

The investigator is not allowed to deviate from the protocol except under emergency circumstances to protect the rights, safety and well-being of study participants. In such cases the emergency deviation shall be documented and reported to the Sponsor and IRB as soon as possible, and no later than 5 working days after the emergency occurred. The Sponsor is required to report such deviation to the FDA within 5 working days after the Sponsor learns of the deviation.

15. Data and Publication Policy

Publications and/or presentation of the clinical investigational results will be coordinated between Pulsar Vascular, Inc. and the clinical investigation author(s). Authorship will be determined prior to development of any manuscript. All information concerning the study, PulseRider device, Sponsor operations, patent application, manufacturing processes, and basic scientific data supplied by the Sponsor to the investigator and not previously published, are considered confidential and remain the sole property of the Sponsor.

16. Study Administration

16.1. Study Leadership

The Pulsar Vascular, Inc. clinical leadership will conduct the clinical study in accordance with Good Clinical Practice Guidelines, including ISO 14155 and FDA regulations, 21 CFR Parts 50, 54, 56, and 812. Pulsar Vascular, Inc. will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants. Together, Pulsar Vascular, Inc. and consultants will ensure that the study is conducted according to all applicable regulations.

16.2. Steering Committee

A Steering Committee comprised of at least three physicians with experience in the areas of neurosurgery, neurology or interventional neuroradiology will be appointed for this study. The responsibilities of the Steering Committee include:

- Consultation on study design, protocol development, patient eligibility inquiries, data to be collected and investigator training
- Review of evidence results (assist in data interpretation)
- Support the Sponsor's efforts in conducting meetings with the regulatory agencies, as appropriate.

17. Conflict of Interest

The term "conflict of interest" refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising a researcher's professional judgment in conducting or reporting research. Pulsar Vascular, Inc. will make every effort to safeguard against conflicts of interest to assure the integrity of the data, subject safety and investigator objectivity.

Clinical investigators will complete financial disclosure forms prior to initiating the study and update them annually or when changes occur related to stock and stock options and income from salary, honorariums, and consulting fees.

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