Clinicaltrials.gov Cover Sheet

THE VESALIO™ NEVA VS FOR THE TREATMENT OF SYMPTOMATIC CEREBRAL VASOSPASM FOLLOWING ANEURYSMAL SUBARACHNOID HEMORRHAGE (ASAH) (VITAL)

Protocol VS-002 / E

NCT03611790

September 23, 2020

SPONSOR
Vesalio
200 West End Ave, Ste 500
Nashville, TN 37203

THE VESALIO™ NEVA VS FOR THE TREATMENT OF SYMPTOMATIC CEREBRAL VASOSPASM FOLLOWING ANEURYSMAL SUBARACHNOID HEMORRHAGE (aSAH) (VITAL)

Protocol VS-002 / E

September 23, 2020

SPONSOR
Vesalio
200 West End Ave, Ste 500
Nashville, TN 37203

INVESTIGATOR'S AGREEMENT

I, the undersigned, am responsible for the conduct of the study at the site below and agree to the following:

- I understand that this protocol is a confidential document. I agree that the information within it will not be disclosed to anyone without prior written authority from the sponsor, Vesalio, except to the extent necessary to conduct this study and obtain approval from the Institutional Review Board (IRB) or other approving body.
- I understand and will conduct the study according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the IRB, except where necessary to prevent any immediate danger to the subject.
- I have sufficient time to properly conduct and complete the study within the agreed study period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.
- I will ensure that any staff members at my site(s) who are involved in the study conduct are adequately trained regarding this trial's operations, the protocol and their responsibilities. In the case of delegating any of my study responsibilities I will provide the sponsor with a delegation of investigators responsibilities log.
- I understand that the study may be terminated, or enrollment may be suspended at any time by Vesalio with or without cause, or by me or my institution if it becomes necessary to protect the best interest of the study subjects.

Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

PROTOCOL TITLE	**The Vesalio™ Neva VS for the Treatment of Symptomatic Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage (aSAH) (The VITAL Study)**
INVESTIGATIONAL DEVICE	NeVa VS device
POPULATION	Subjects aged ≥ 18 years presenting with symptomatic cerebral vasospasm despite maximal medical management following aSAH.
STUDY DESIGN	A prospective, open label, single-arm study designed to assess the safety and probable benefit of the Neva VS device in patients presenting with symptomatic cerebral vasospasm following aSAH. Up to 150 eligible subjects at up to 15 sites will participate in the study. Safety will be monitored throughout the study and assessed regularly by an independent Data Safety Monitoring Board (DSMB).
STUDY OBJECTIVES	The objective of the study is to assess the safety and probable benefit of the Neva VS device in patients presenting with symptomatic cerebral vasospasm despite maximal medical management following aSAH. Outcomes include safety, procedural success and clinical improvement.
INCLUSION CRITERIA	1. Age ≥ 18 years. 2. Subarachnoid hemorrhage secondary to ruptured aneurysm. 3. Ruptured aneurysm secured with surgical clipping or endovascular intervention. 4. Digital subtraction angiography (DSA) or CT angiography at the time of aSAH clinical presentation or aSAH intervention with well-visualized intra-cerebral vessels is available for review. 5. Vasospasm in one or more of the following: the internal carotid artery (ICA), basilar, middle cerebral artery (MCA), anterior cerebral artery (ACA), or posterior cerebral artery (PCA) territory on transcranial Doppler (TCD), and/or CT angiography, **and/or** clinical signs of symptomatic vasospasm (change in level of consciousness, focal neurological deficit) **confirmed by** > 50% stenosis in these territories on DSA. 6. Vasospasm despite maximized medical management defined as oral Nimodipine (unless contraindicated), systemic hypertension with systolic blood pressure (SBP) greater than 130 mmHg and euvolemia.

7. Target vessel pre-vasospasm diameter ≥ 2.0 mm and ≤ 4.0 mm.
8. Subject or legal representative is able and willing to give informed consent.

EXCLUSION CRITERIA

1. The presence of an unsecured ruptured aneurysm. *Note unsecured unruptured aneurysms remote to the site of treated aSAH are not an exclusionary*.
2. Symptoms attributable to other causes (e.g., hydrocephalus, metabolic, infection).
3. Hunt and Hess Grade of 5
4. Large infarct on CT scan defined as ASPECTS 0-5.
5. Intracranial hemorrhage not caused by aneurysm rupture.
6. History of bleeding disorders.
7. Baseline platelets < 30,000
8. International normalized ratio (INR) > 1.7.
9. Any known contraindications to mechanical dilation of vasospastic vessels including but not limited to:

    - Excessive vessel tortuosity that prevents the placement of the device
    - Evidence of rapidly improving neurological signs of stroke
    - Large territory completed cerebral infarction, edema with mass effect and intra-parenchymal hemorrhage in vascular territory to be treated, or
    - any other vascular anatomic variants or anomalies

10. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. dementia with prescribed anti-cholinesterase inhibitor (e.g. Aricept).
11. History of severe allergy to contrast medium.
12. Known allergy to NeVa materials (nitinol, stainless steel).
13. Suspected or confirmed septic embolus, or bacterial endocarditis.
14. Septic shock or central nervous system (CNS) infection confirmed via cerebrospinal fluid (CSF) sampling.
15. Known current or recent use of illicit drugs or alcohol abuse.
16. Females who are pregnant or breastfeeding.
17. Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the subject if an endovascular procedure is performed.

STUDY PROCEDURES

Screening should be completed within 21 days post initial ictus (aSAH). Due to the emergent nature of vasospasm, all patients admitted with SAH secondary to a ruptured aneurysm that was secured with surgical clipping or endovascular intervention with a Hunt and Hess Scale grade of 4 or less will proceed with screening.

Prior to screening, subjects (or their legal representative) will give informed consent. Screening procedures include relevant medical history, vital signs, pre-hospital and current modified Rankin Scale (mRS), NIH Stroke Scale (NIHSS), non-contrast head CT-scan (NCCT) to determine ICH, concomitant medications, coagulation panel, and urine pregnancy test (unless already conducted at hospital admission; women of childbearing potential only). Laboratory testing does not need to be repeated if testing was performed within the past 72 hours. The modified Fisher grade and Hunt-Hess grading system at time of aSAH will be documented.

Note, the site will determine eligibility based on the in/exclusion criteria listed above. Although, the core lab will assess specific parameters at Screening that are part of the eligibility criteria, the assessment by the Core Lab is for consistency across study participants and sites.

On Day 0, (day of the NeVa VS intervention), subjects with confirmed vasospasm (defined as > 50% stenosis in the ICA, basilar, MCA, ACA, or PCA territory as demonstrated by DSA or CTA) within 21 days post SAH ictus will be eligible to undergo the interventional procedure. All study images will be sent to the Core Lab.

Eligible subjects will be treated with the appropriate sized NeVa VS device in all suitable affected vessels. The NeVa VS device is a percutaneously introduced transluminal cerebral vasodilatation device that is temporarily inserted into the cerebral vasculature for the dilation of targeted spastic vessels with controlled expansive radial force. The Neva VS device will be navigated into the affected vascular territory and deployed in the most distal size compatible segment. The Neva VS device will be deployed from a distal location to proximal location by unsheathing and re-sheathing the device, retracting the microcatheter and unsheathing and re-sheathing more proximally until the entire size compatible, affected area has been treated. A final DSA will be performed at the end of the procedure to characterize the degree of narrowing in the treated portion of the target vessel. Procedural complications and procedural success will be documented. Use of any balloon angioplasty intervention as a rescue therapy is off-label and prohibited in this study.

At 24-hours (±6 hours) post intervention, a non-contrast head CT scan and TCD will be obtained as indicated. In addition, a NIHSS will be obtained. Vital signs, concomitant medications, and adverse events will also be assessed.

	At Day 21 post aSAH or hospital discharge (whichever occurs first), a non-contrast head CT-scan, TCD, NIHSS, mRS will be obtained. Concomitant medications, and adverse events will be assessed. At Day 30 (± 7 days) post intervention (treatment with NeVa VS), mRS, and adverse events will be assessed. If vasospasm recurs in a previously treated segment or in another (different) vessel / territory or different segment of a previously treated vessel after treatment of the initial vasospasm segment (s) but prior to hospital discharge, treatment with the NeVa VS is allowed if the subject still meets all study entry criteria. If a subject is retreated, he or she will be followed up for 30 more days per the retreatment schedule in Appendix 1. All treated areas will be imaged accordingly.
CONCOMITANT MEDICATIONS / PROCEDURES	Subjects for whom oral nimodipine is indicated are treated with oral nimodipine at standard dose of 60mg PO/NGT Q 6 hours without prevention of the development of vasospasm. Use of any balloon angioplasty intervention as a rescue therapy is off-label and prohibited in this study.
SCHEDULE OF EXAMINATIONS	Screening (Day 0 to 21 post-aSAH) Day 0 – NeVa VS intervention (within 21 days post aSAH) 24 hrs ± 6 hrs post NeVa VS intervention Day 21 ± 2 days post aSAH or discharge (whichever occurs first) Day 30 post initial intervention with NeVa VS ± 7 days
STUDY OUTCOMES	• ***Procedural Success*** - defined as 50% or greater vessel caliber on DSA compared to baseline, as determined by the core laboratory. • ***Retreatment / additional treatment*** – the rate of retreatment or treatment of additional territories will be quantified. • ***Symptomatic Improvement*** - for clinically symptomatic patients, a decrease at 24 hours of ≥ 3-points from Screening as measured by NIHSS and/or resolution of pre-procedural clinical deficits. • ***Change in ASPECT Score*** –change in ASPECT score on NCCT from Screening to Day 21 post aSAH or discharge, whichever occurs first • ***Clinical Status*** – Change in modified Rankin Scale score from Screening at Day 30
SAFETY	All subjects that have a Neva VS device introduced into their vasculature (regardless of the ability to reach the target location) will be included in the safety analysis population. Adverse events

(including serious adverse device effects, procedure related serious adverse events, and any adverse events leading to treatment discontinuation) throughout the 30-Day follow-up will be described according to severity and to their relationship with the study device and procedure. Descriptive statistics (N, mean, median, SD, minimum and maximum values, where applicable) will be used to characterize safety parameters.

TABLE OF CONTENTS

FIGURES & TABLES

TABLE OF APPENDICES

ABBREVIATIONS

ACA	Anterior Cerebral Artery
AE	Adverse Event
aSAH	Aneurysmal Subarachnoid Hemorrhage
ASPECTS	Alberta Stroke Program Early CT score
β-HCG	Beta Human Chorionic Gonadotropin
BioMDG	Biologics and Medical Device Consulting Group
CFR	Code of Federal Regulations
CNS	Central Nervous System
CRO	Clinical Research Organization
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CV	Cerebral Vasospasm
DCI	Delayed Cerebral Ischemia
DHHS	Department of Health and Human Services
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HDE	Humanitarian Device Exemption
HIPAA	Health Insurance Portability and Accountability Act
ICA	Internal Carotid Artery
ICH	Intracranial Hemorrhage
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
IVH	Intraventricular hemorrhage
LMW	Low Molecular Weight
MCA	Middle Cerebral Artery
mRS	Modified Rankin Scale
NCCT	Non-Contrast CT
NIH	National Institutes of Health
NIHSS	NIH Stroke Scale
NO	Nitric Oxide
PCA	Posterior Cerebral Artery
PI	Principal Investigator
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RNS	Reactive Nitrogen Species
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
TCD	Transcranial Doppler
UADE	Unanticipated Adverse Device Effect

PERSONNEL AND FACILITIES

STUDY SPONSOR	Vesalio (dba of Legacy Ventures LLC) 3200 West End Ave Suite 500 Nashville, TN 37203
MEDICAL MONITOR	Jonathan J. Ratcliff, MD, MPH Assistant Professor, Department of Emergency Medicine, Emory University, School of Medicine 49 Jesse Hill Jr Dr Atlanta, GA 30303
INVESTIGATORS	Principal Investigator (for entire study): Dr. Arthur John Ulm III Nashville Neurosurgery Associates 330 22nd Avenue North Nashville, TN 37203 Other Investigators: TBD
IMAGING CORE LAB	Dr. David Liebeskind, MD, FAAN, FAHA, FANA Professor of Neurology and Director, Neurovascular Imaging Research Core UCLA Department of Neurology Neuroscience Research Building 635 Charles E Young Drive South, Suite 225 Los Angeles, CA 90095-7334
CLINICAL RESEARCH ORGANIZATION (CRO)	Biologics and Medical Device Consulting Group (BioMDG) 20370 Skyhawk Lane Topanga, CA 90290 Phone: (310) 455-3473 Fax: (888) 295-1535

1. DELAYED CEREBRAL ISCHEMIA DUE TO SYMPTOMATIC CEREBRAL VASOSPASM FOLLOWING ANEURYSMAL SUBARACHNOID HEMORRHAGE (aSAH)

In the US, the annual incidence of all strokes is 795,000. Eighty-seven percent (87%) are ischemic, 10% are intracranial hemorrhage (ICH) strokes, and 3% are SAH strokes.[1] Eighty-five percent (85%) of SAH is aneurysmal, with the remaining attributed to traumatic brain injury, vascular malformations, and to inflammatory and non-inflammatory lesions.[2] The 24-hour mortality rate for aneurysmal SAH (aSAH) is 20%, with 10% - 15% acute mortality before reaching the hospital, and 10% mortality within 24 hours of hospitalization.[1,3,4] The majority of patients who survive to hospitalization are treated using either an endovascular intervention (coiling) or by surgical clipping. Delayed cerebral ischemia (DCI) can occur in up to 45% of patients 3-14 days post-intervention.[5-20] It is thought to be caused by the combined effects of vasospasm, arteriolar constriction and thrombosis, cortical spreading ischemia, and neuroinflammatory processes triggered by the initial ictus,[11,21-23] and accounts for almost 50% of the deaths following aSAH.[24-26]

1.1. PATHOPHYSIOLOGY

Cerebral vasospasm (CV) is strongly associated with DCI, and, although it is not the only contributing factor to poor clinical outcomes, it is the most important and potentially treatable cause of morbidity and mortality after aSAH. As in other body systems, (e.g. coronary artery vasospasm), vasospasm of arteries in the brain is thought to be precipitated by a confluence of multiple pathological processes that result in a reduction of nitric oxide (NO) bioavailability. NO has a direct vasodilation effect and plays a significant role in modulating endogenous vasoconstrictive agents (e.g. production and release of endothelin-1 [ET-1] and thromboxanes), and in mediating the inflammatory response.[27]

In the coronary arteries, vasospasm may occur because of ischemic conditions, endothelial cell damage, and oxidative stress. In the brain, the main driver of vasospasm is thought to be the release of ferrous hemoglobin and erythrocyte contents through hemolysis during the initial ictus. NO is upregulated in response to the insult. However, the large amount of extracellular hemoglobin and other blood products in the subarachnoid space are thought to reduce NO bioavailability by acting as an NO "sink". Additionally, in the context of this exaggerated inflammation, excess NO production can be harmful. Reactive nitrogen species (RNS), especially peroxynitrite, are capable of disrupting cellular metabolism, irreversibly damaging DNA, and ultimately causing cell death and damage to the adjacent cortex.[27-29] Together with the net reduction in bioavailable NO, and the continued release of vasoconstrictive agents, voltage gated calcium channels are opened causing the smooth muscle in the arteries to contract.[30]

The severity of the vasospasm is related to volume, density and persistence of the initial subarachnoid thrombus, the degree of early brain injury, and to other underlying conditions that can reduce brain oxygen.[31] Severe vasospasm (> 50% narrowing) within the DCI window (at approx. day 7 post ictus) is highly suggestive of poor clinical outcomes.[15,31,32] Prophylactic treatment with calcium channel blockers (both oral and targeted infusion) are often administered with the aim of

preventing smooth muscle depolarization and subsequent vasospasm. However, the only drug approved for this specific indication, oral nimodipine, is largely ineffective,[33] perhaps because it does not address the local reduction in bioavailable NO or the presence of other vasoactive agents.

1.2. CURRENT TREATMENT OPTIONS

Current standard of care for treatment of patients post aSAH is geared towards prevention of secondary DCI, particularly by detecting and reducing the incidence of vasospasm.[15,24,25,34-37] The only FDA approved drug for the treatment of aSAH is oral nimodipine (tablet and suspension) and it is a class I recommendation. †[24,25,33] Targeted intraventricular infusion and intravenous nimodipine have been granted orphan status (5/28/2015 and 8/10/2017, respectively) and have shown some efficacy, but neither approach has been approved.[38-40] Use of other vasodilators such as verapamil and milrinone have shown some level of success, but are not specifically approved for this indication.[24,25,41] Although not approved for this use by FDA, its use is common and is part of the standard of care guidelines issued over the decades by the American Heart Association.[24,42,43] Hyperdynamic therapy with induced hypertension, and augmentation of cardiac output using inotropic drugs has also shown some efficacy.[24,25,41] Intra-arterial treatments such as luminal angioplasty are conducted using cardiac devices off-label [(Sprinter Legend balloon (Medtronic), Maverick (Boston Scientific), Gateway (Boston Scientific) and Scepter XC (Microvention)] with some success.[44-46] NeuroFlo, a dual aortic balloon device was developed specifically for treatment of DCI by diverting blood flow to the brain and was approved under HDE H030005, but is no longer available in commercial distribution.

1.3. UNMET CLINICAL NEED

DCI continues to occur in up to 45% of patients post aSAH despite maximal medical care. It is associated with a substantial burden on health care resources, most of which are related to long-term care and loss of productivity, as half of the patients affected are under the age of 55.[1,2,9,11,47]

1.4. MECHANICAL DILATATION FOR PREVENTION OF VASOSPASM

Cerebral angioplasty conducted with a variety of endovascular catheters has demonstrated improvement, and occasionally, permanent reversal of vasospasm in treated vessels.[44-46,48-53] Arterial dilatation was first discussed in the peer-reviewed literature in 1984,[54] and has steadily gained acceptance as a viable treatment option for patients that fail maximal medical therapy. Due to the low incidence of this condition, however, cerebral angioplasty has not been studied in an adequately powered controlled randomized study. Nonetheless, the reported neurological

† See approved labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018869s014lbl.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203340lbl.pdf)

improvement rates using this treatment strategy are far better than the documented natural history of the disease.

Physiological Effect of Mechanical Dilatation. Circumferential dilation of an artery causes a 'controlled injury.' The stretch can cause endothelial denudation, fracture of the intima, medial thinning and tearing of the adventitia. These mechanical effects alter the connections between the smooth muscle cells in the media and their elastic fibers.

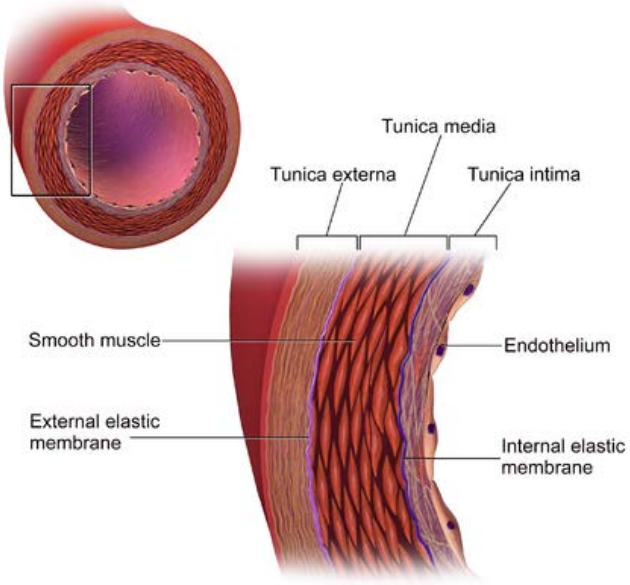


Figure 1. Arterial anatomy

Several studies have demonstrated that arterial dilatation decreases arterial contractility and some have seen arterial paralysis.[55] Arterial dilatation may largely be efficacious because of the disconnection of the endothelium from the media and because of the disruption of connective tissues that proliferate in the vessel wall after a subarachnoid hemorrhage. The effect is both mechanical and biochemical. The mechanical overstretching causes a paralytic injury,[56,57] while the disconnection of the endothelium eliminates the local release of endothelium derived vasoconstricting factors (e.g. ET-1, thromboxanes) and disrupts the calcium channel inputs into the media.[58]

Current Procedural Limitations. There are no commercially available, FDA-approved devices available for the treatment of CV, and devices used off-label can only be safely deployed in the most proximal vessel segments; internal carotid and vertebrobasilar arteries and the first segment of the middle cerebral artery (MCA). Accessing and treating vasospasm in the anterior cerebral arteries, M2 MCA and Posterior cerebral arteries is more problematic and associated with higher complication rates. Fatal arterial ruptures, branch occlusion, displacement of aneurysm clip or re-rupture of a treated aneurysm during balloon dilation have been

reported.[26,44,59] In addition, because balloon dilation is an occlusive process, the procedure may further harm an already ischemic brain.

Stent Retriever Based Angioplasty - A New Approach for Managing CV. The use of stent retrievers (stentrievers) to cause vasodilation in patients with delayed cerebral vasospasm secondary to subarachnoid hemorrhage was recently published.[60] The small proof of concept case series (4 patients) reported the use of the Solitaire and Capture stent retrievers to safely achieve vasodilation with long-lasting therapeutic effect (> 24 hours). In two of the cases, stent angioplasty resulted in a reversal of focal neurological symptoms.

The advantages of using a stent retriever over a balloon to dilate spastic cerebral arteries post aSAH include:

- better maneuverability and safer deployment into distal and posterior segments;
- controlled dilation using the intrinsic outward radial force, (as opposed to a fixed diameter expansion in balloon angioplasty which is operator dependent and can result in vessel rupture); and
- the intervention is conducted without occluding blood flow to already severely compromised ischemic tissues.

1.5. STUDY GOALS

The objective of this study is to assess the safety and probable benefit of the NeVa VS device (a modified stent retriever) in patients presenting with symptomatic cerebral vasospasm despite maximal medical management following aSAH.

2. NEVA VS DEVICE DESCRIPTION AND PRINCIPLES OF OPERATION

The Vesalio NeVa™ VS device is a neuro mechanical percutaneously introduced transluminal cerebral dilatation device. The design of the NeVa VS is based on the common design for stentrievers (e.g., TREVO Retrievers (DEN150049) and Solitaire Revascularization Device (K162539)).

2.1. DEVICE DESCRIPTION

The NeVa VS device has a self-expanding nitinol stent-like scaffolding tip attached to a nitinol push wire. The device can only be delivered through a Trevo Pro 18 Microcatheter.

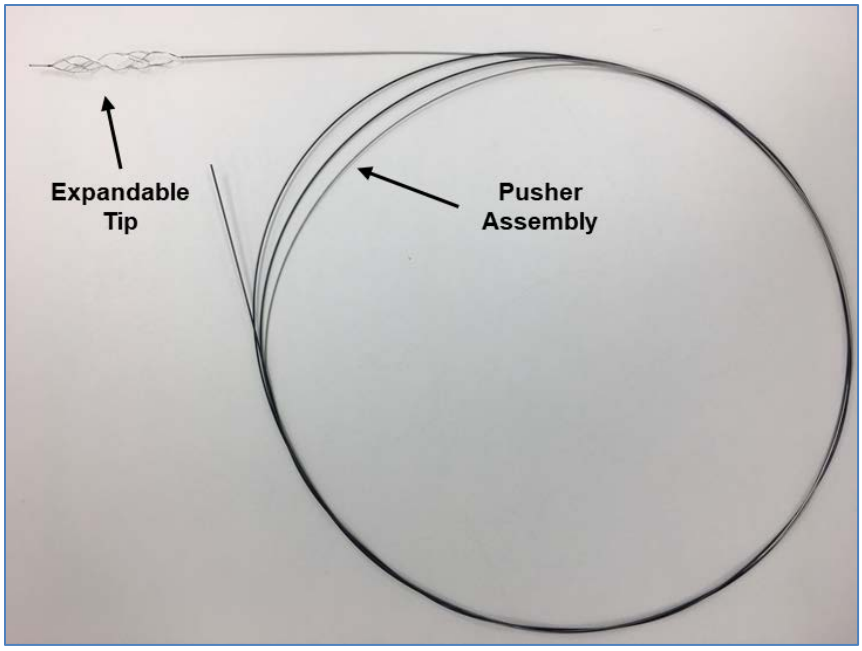


Figure 2. NeVa VS device

When deployed at the target treatment area, the tip (which was compressed in the microcatheter), expands into its original shape in the artery and applies expansive radial forces to the wall of the artery. The NeVa VS can be deployed in the M1 and M2 branches of the middle cerebral artery (MCA), intracranial internal carotid artery (ICA), intracranial vertebral artery, basilar artery, and the P1 posterior cerebral artery (PCA).

The device is provided sterile and is intended for single-use only.

2.1.1. THE EXPANDABLE TIP

The expandable tip on the distal end of the NeVa VS is constructed of a tubular scaffolding laser cut from Nitinol tube stock. It has tapered distal and proximal ends and a proprietary scaffolding design to optimize expansive radial forces for effective dilation force. Figure 3 depicts the closed cell configuration in its expanded state.

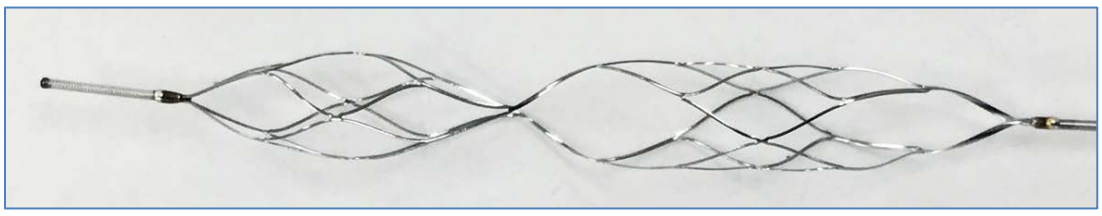


Figure 3. NeVa VS Expandable tip

The total length of the NeVa VS tip is 35 mm, the length of the fully expanded diameter is 22 mm with 4mm of gradual taper on either side. The expanded outside

diameter is 4 mm and the device configuration can be deployed in vessels with a pre-vasospasm diameter from 2.0 – 4.0 mm.

The design of the expandable tip integrates the following set of key features:

- Radiopaque markers positioned on the structure at proximal and distal ends to ensure fluoroscopic visualization during placement;
- Gradual double ended taper as opposed to a uniform diameter (as seen in other stent retrievers) to allow for a more distal deployment in a vessel;
- Two central twisting tethers in the middle of the tip (see Figure 4). This feature provides enhanced flexibility and maneuverability, particularly if the vasospasm is occurring in a branched segment of the vasculature.

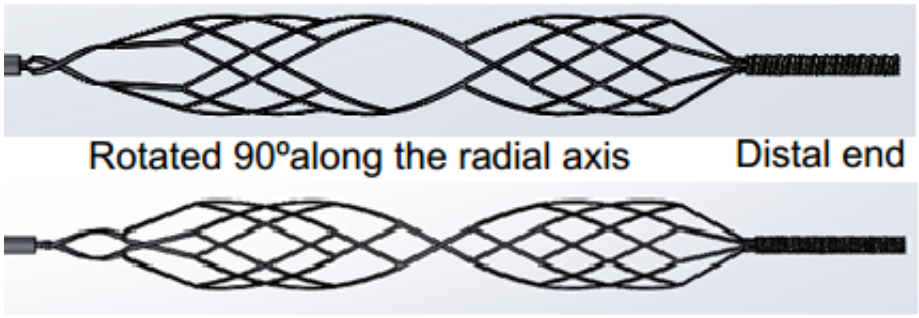


Figure 4. NeVa VS Central twisting tether design

Two versions of the NeVa VS are available. They only differ in the configuration of radiopaque markers for fluoroscopic visualization on the tip. Both versions have a 1 mm radiopaque marker coil (92% Platinum/ 8% Tungsten) at the proximal end. Both also have a radiopaque marker coil on the distal end. The standard NeVa VS has the same 1 mm radiopaque marker on the distal end as on the proximal end. The enhanced visualization version has an extended radiopaque marker coil that is 5 mm in length (same materials and radial dimensions, only 4 mm longer). An illustration of the two (2) distal end marker coils is provided in Figure 5.

Figure 5. NeVa VS Distal marker configurations (a) standard (b) extended

Both distal radiopaque markers (standard and extended) provide visual indication under fluoroscopy, however, the extended marker is available for clinicians that prefer enhanced visualization.

2.1.2. PUSHER ASSEMBLY

The pusher assembly is comprised of an introducer and delivery pusher that are used to deliver the expandable tip to the treatment site.

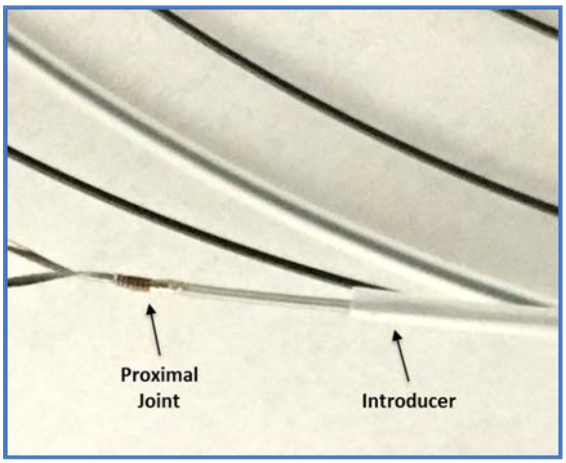


Figure 6. NeVa VS Pusher Assembly

The introducer consists of a polymer tube that protects the device and distal segment of the delivery pusher from damage. When firmly seated in the hub of the microcatheter, the introducer creates an uninterrupted passage for the device to be advanced through the microcatheter.

2.2. PROPOSED INDICATIONS FOR USE

The NeVa VS is intended for the treatment of aneurysmal subarachnoid hemorrhage patients who experience symptomatic vasospasm despite maximal medical management.

2.3. PRINCIPLES OF OPERATION

The NeVa VS is a percutaneously introduced transluminal cerebral artery dilatation device that is temporarily inserted into the cerebral vasculature for the dilation of targeted vessels to treat SAH induced vasospasm. The overall operation and deployment of the NeVa VS follows the same basic principles and procedures as for use of stentrievers. However, instead of deploying the expandable tip to remove a thrombus, deployment of the expandable tip is intended to apply a controlled expansive radial force to dilate a spastic artery. Following is a description of the device operation. A discussion of the scientific rationale for mechanical dilatation for the treatment of CV can be found in Section 1.4.

1) A suitable guide catheter is placed in the vessel close to the targeted site(s). Using an appropriate guidewire, a microcatheter is advanced to the target vessel and then the catheter tip is positioned distal to the target site with sufficient space to deploy the NeVa VS into the target vessel. The guidewire is retrieved, and the position of the catheter is confirmed used angiographic techniques.

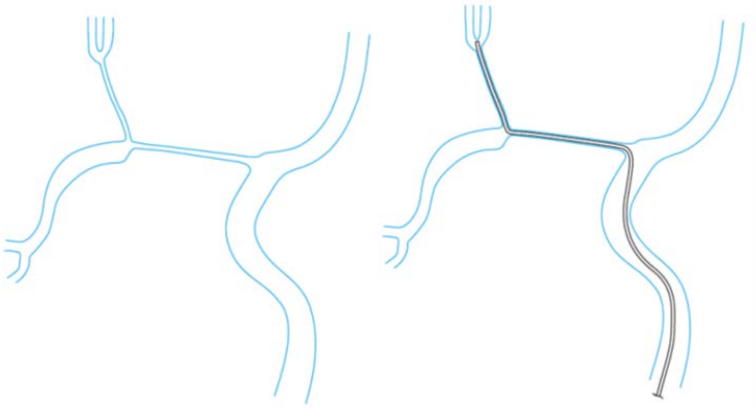


Figure 7. Microcatheter Navigation to the Target Vessel

2) The NeVa VS device is transferred into the microcatheter and then advanced within the catheter using the push wire. With aid of fluoroscopic monitoring, the NeVa VS expandable tip is advanced until its distal markers line up with the end of the catheter.

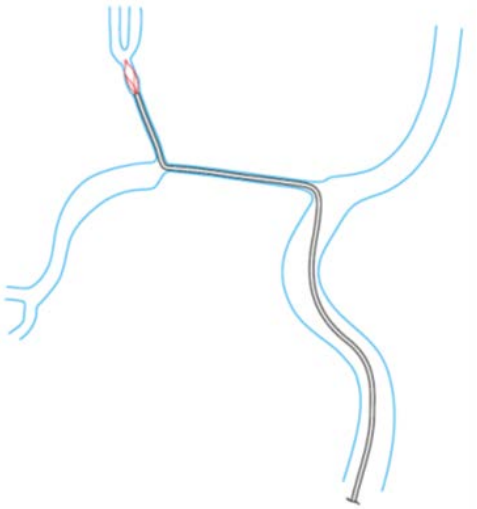


Figure 8. Advancement of the NeVa VS in a Target Vessel

3) The NeVa VS is deployed by fixing the push wire in place and withdrawing the microcatheter in the proximal direction. The catheter is retracted until the catheter tip is just proximal of the proximal marker on the expandable tip.

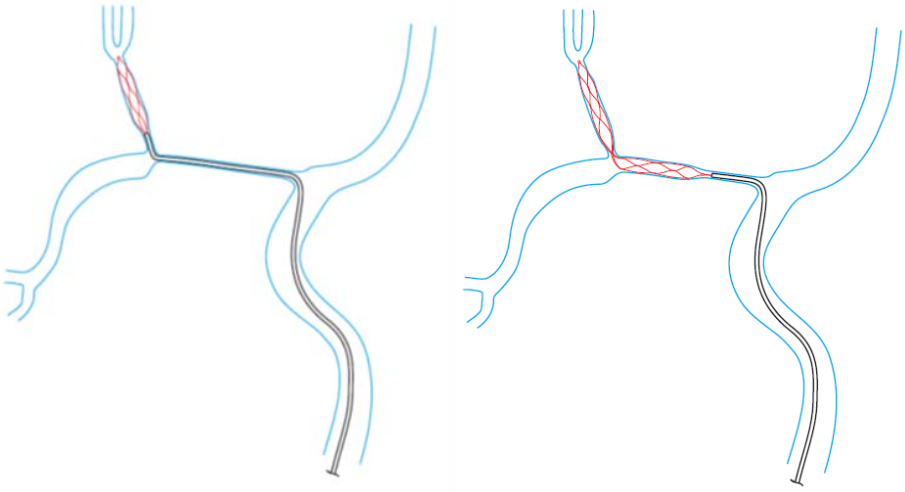


Figure 9. Deployment of the NeVa VS in a Target Vessel, including placement in artery branch (right)

4) Once deployed in the target vessel, the scaffolding structure of the NeVa VS tip intrinsically expands, providing a slow, controlled dilation.

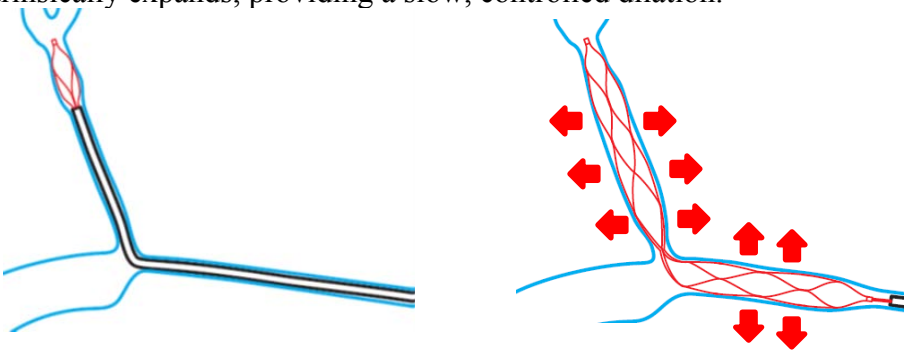


Figure 10. Example of Dilation Forces with the NeVa VS

5) As needed, the stent can be resheathed back into the microcatheter and redeployed in the target vessel at additional multiple locations based on the judgement of the healthcare provider.

6) After sufficient deployments of the stent have been performed in the target vessel, the device is retrieved into guide catheter as the device is completely retracted.

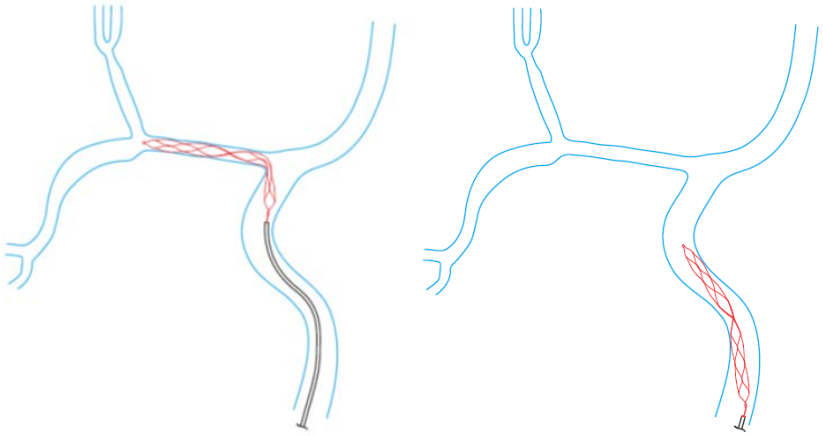


Figure 11.Serial Segment Vessel Dilation with the NeVa VS

2.3.1. VASODILATION WITH THE NEVA VS

The NeVa VS device design is a modification of the stent retrievers currently available in commercial distribution (Solitaire, Trevo) which have been safely used for a number of years for mechanical thrombectomy in ischemic stroke. The design features of the NeVa VS are compared to these stentrievers in Table 1.

Table 1. Feature Comparison Between the NeVa VS, and the Commercially Available Solitaire, and Trevo Stent Retrievers

Design Features	NeVa VS	Solitaire		Trevo
Size*	4-22	6-30	4-20	4-20
Expansion diameter	4.0 mm	6.0 mm	4.0 mm	4.0 mm
Distal Tip	tapered	uniform	uniform	uniform
Compressive radial force (N/mm)†	1.7 – 3.8	1.9 - 4	1.13-2.51	2 - 3.5
Expansive radial force (N/mm) †	1 – 1.9	0.6 – 1.4	0-.058	0.4 – 1.2
Segmented design which allows deployment at a branching point in the artery	yes	no	no	no

* For each device, the first value refers to the nominal diameter, the second value refers to the length expressed in mm

† Bench testing results

Unlike other stent retrievers which have a uniform diameter across the stent segment that cause a 'ledge' effect at the interface with the spastic segment, the NeVa VS's tapered distal end provides a more gentle and anatomically conforming dilatation process.

Current stent retrievers also have a high compressive radial force (the force required to externally compress the device) and a very low expansive radial force (force of stent expanding upon deployment), particularly at diameters over 2mm. The NeVa

VS was engineered to have a similar compressive radial force as other stent retrievers, but a greater expansive radial force at every diameter of expansion across the indicated range. This allows for more effective dilation force than other stentrievers, a stated deficiency in standard stentrievers design noted in the feasibility study discussed earlier in this section.[60] Further, by limiting the dilation force to the intrinsic outward radial force of the device (in contrast to balloon catheters which can be expanded to a pre-fixed diameter) and performing the dilation over longer periods up to several minutes (as opposed seconds for a balloon catheter), the potential for injury to the vessel is reduced.

Finally, two additional design enhancements make the NeVa VS more suitable for treating CV:

- The NeVa VS has two large twisting tethers in the middle of the stent which allow the device to be deployed into two branch points around bends in the artery without causing significant deformation. And,
- the NeVa VS has a proximal taper which allows the deployed device to be withdrawn from a distal position to a more proximal position and to sequentially dilate the vessel.

2.3.2. PRECLINICAL DATA

The ability of the NeVa VS to safely dilate vasospastic arteries was demonstrated in a small GLP study in the juvenile porcine model. Three (3) Yorkshire crossbred pigs were used as the animal model for the study. The porcine model was chosen because the animals have similar arterial sizes as humans and have similar hemodynamic properties that could affect device use. In addition, the selected animal model has similar vessel wall thickness, smooth muscle reactivity, and clotting processes to humans. Two (2) of the animals were used for acute evaluation and one (1) for chronic evaluation.

The following test and control devices were tested as part of this study:

- NeVa VS (test article)
- Trevo XP 4x20 stent retriever (control article)
- Maverick angioplasty balloon (control article)

Three (3) test articles and three (3) control articles were deployed in separate target arteries in each animal. NeVa VS test articles were deployed in all three (3) animals, two (2) for acute and one (1) for chronic evaluation. The Trevo XP was deployed in a single animal for acute comparison to the NeVa VS and the Maverick balloon catheter was deployed in two (2) animals for both acute and chronic comparison to the NeVa VS.

There were no complications noted during insertion, deployment, or retraction for any of the test or control articles deployed. A total of 54 deployments with the NeVa VS test article were performed evenly over 9 arteries (across 3 animals). For

the Maverick control article, a total of 36 deployments were performed evenly over 6 arteries (across 2 animals). With the Trevo control article, a total of 18 deployments were performed over 3 arteries (a single animal). No mechanical damage was observed with any of the test or control articles during the procedure. There were no incidents of vessel perforation. All three (3) animals remained stable under anesthesia without complications and survived to the end of the procedure.

After deployment of each test and control article at the treatment sites, various degrees of spasm were observed. Overall for the NeVa VS, spasm was temporary in all cases and recovered to a baseline level (Score = 0) in 7 of 9 treatment sites and to a Score = 1 (10% slight narrowing) and Score = 2 (27% moderate narrowing) for the two remaining sites. In comparison, for the Trevo controls all three treatment sites only recovered to a Score = 1 (21%, 24%, and 23% narrowing) and for the Maverick controls only 1 of 6 recovered to a baseline level, with two (2) of the sites recovering to a Score of 1 and the remaining three (3) sites recovering to a Score = 2. Mean vessel scores after 60 minutes were 0.33 for NeVa VS, 1.0 for Trevo, and 1.33 for Maverick devices. Based on these results, the arteries treated with the NeVa VS exhibited a lower level of vasospasm. In general, swine arteries are susceptible to vasospasm, and the results seen here are comparable with other thrombectomy devices used in swine. This expected result was determined to not pose a significant safety risk.

Histological findings did not reveal any significant downstream tissue effects. In addition, observations from the pathological evaluation demonstrate that the NeVa VS had lower or similar scores for minor and superficial injuries to treatment vessels than the other devices. Based on the results of the study, the deployment of the NeVa VS appears to be safe with no evidence of downstream effects and successfully meets the usability criteria for the device.

3. GOOD CLINICAL PRACTICES (GCP) STATEMENT

This trial will be conducted in compliance with all applicable federal regulations pertaining to investigational drugs and devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 812, and GCP standards. This trial will be conducted in compliance with the protocol as approved by an Institutional Review Board (IRB). Any deviations from the protocol that may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the IRB per each institution's guidelines.

4. INVESTIGATIONAL PLAN

4.1. STUDY OBJECTIVES

The objective of the VITAL Study is to assess the safety and probable benefit of the Neva VS device (a modified stent retriever) in patients presenting with symptomatic cerebral vasospasm despite maximal medical management following aSAH.

Outcomes include safety, procedural success and clinical improvement.

4.2. STUDY DESIGN

This is an open-label, single-arm, multicenter, 30-day study designed to assess the safety and probable benefit of the Neva VS device in patients presenting with symptomatic cerebral vasospasm following aSAH. Up to 150 eligible subjects at up to 15 sites will participate in the study.

Test results from routinely performed standard of care assessments in aSAH management may be used to determine eligibility. Therefore, pre-screening without obtaining informed consent is allowed. Due to the emergent nature of vasospasm, all patients admitted with SAH secondary to a ruptured aneurysm that was secured with surgical clipping or endovascular intervention with a Hunt and Hess Scale grade of 4 or less will proceed with screening.

The study will be thoroughly explained to the subject or his/her legal representative in order to obtain informed consent. Informed consent can be obtained prior to onset of vasospasm. Screening must be completed within 21 days post SAH ictus.

Screening will include assessment of study eligibility, relevant medical history, vital signs, pre-hospital and current modified Rankin Scale (mRS), NIH Stroke Scale (NIHSS), non-contrast head CT-scan (NCCT) to determine ICH, concomitant medications, coagulation panel, and urine pregnancy test (unless already conducted at hospital admission; women of childbearing potential only). Laboratory testing does not need to be repeated if testing was performed within the past 72 hours. The modified Fisher grade and Hunt-Hess grading system at time of aSAH will be documented.

Patients who subsequently experience vasospasm in the ICA, basilar, MCA, ACA or PCA territory on TCD and/or clinical signs of symptomatic vasospasm (change in level of consciousness, focal neurological deficit) will be eligible to participate in the study.

Note, the site will determine eligibility based on the in/exclusion criteria listed above. Although, the core lab will assess specific parameters at Screening that are part of the eligibility criteria, the assessment by the Core Lab is for consistency across study participants and sites.

On Day 0, (day of the NeVa VS intervention), subjects with confirmed vasospasm (defined as > 50% stenosis in the ICA, basilar, MCA, ACA, or PCA territory as demonstrated by DSA or CTA) within 21 days post SAH ictus will be eligible to undergo the interventional procedure. All study images will be sent to the Core Lab. Eligible subjects will be treated with the appropriate sized NeVa VS device in all affected vessels.

The interventional procedure with the NeVa VS device will be performed as follows:

The NeVa VS device is a percutaneously introduced transluminal cerebral vasodilatation device that is temporarily inserted into the cerebral vasculature for the dilation of targeted spastic vessels with controlled expansive radial force. The Neva VS device will be navigated to the most distal size compatible location of the affected area. It will be deployed from distal location to proximal location by unsheathing and re-sheathing the device, retracting the microcatheter and unsheathing and re-sheathing more proximally until the entire size compatible affected area has been treated. A final DSA will be performed at the end of the procedure to characterize the degree of narrowing in the treated segment(s) of the target vessel. Procedural complications and procedural success will be documented.

At 24-hours (± 6 hours) post intervention, imaging to determine ICH (NCCT), TCD and NIHSS will be obtained. Vital signs, concomitant medications, and adverse events (AEs) will also be assessed.

If vasospasm recurs in a previously treated segment or in another (different) vessel / or a previously treated vessel segment or territory after treatment of the initial vasospasm but prior to hospital discharge, treatment with the NeVa VS is allowed if the subject still meets all study entry criteria. If a subject is retreated, he or she will be followed up for 30 more days per the retreatment schedule in Appendix 1. All treated areas will be imaged accordingly.

At Day 21 (± 2 days) post aSAH or hospital discharge (whichever occurs first), imaging to determine ICH (NCCT), TCD, NIHSS, mRS will be obtained. Concomitant medications, and adverse events will be assessed.

At Day 30 (± 7 days) post intervention (initial treatment with NeVa VS), mRS, and adverse events will be assessed.

Note, all non-contrast CT or MRI (if obtained), CTA and DSA acquired during the index hospitalization will be transmitted to the core lab for review.

A summary of the schedule of evaluations and visits can be found in Appendix 1.

4.3. SUBJECT POPULATION

Up to 150 subjects with aSAH meeting the following study entry criteria will be enrolled and treated.

4.3.1. INCLUSION CRITERIA

Subjects must satisfy all inclusion criteria to be included in the study:

1. Age ≥ 18 years.
2. Subarachnoid hemorrhage secondary to ruptured aneurysm.
3. Ruptured aneurysm secured with surgical clipping or endovascular intervention.
4. Baseline digital subtraction angiography (DSA) or CT angiography at the time of aSAH clinical presentation or aSAH intervention with well-visualized intra-cerebral vessels is available for review.
5. Vasospasm in one or more of the following: the internal carotid artery (ICA), basilar, middle cerebral artery (MCA), anterior cerebral artery (ACA), or posterior cerebral artery (PCA) territory on transcranial Doppler (TCD), and/or CT angiography, **and/or** clinical signs of symptomatic vasospasm (change in level of consciousness, focal neurological deficit) **confirmed by** > 50% narrowing in these territories on DSA.
6. Vasospasm despite maximized medical management defined as oral Nimodipine (unless contraindicated), systemic hypertension with SBP greater than 130 mmHg and euvolemia.
7. Target vessel pre-vasospasm diameter ≥ 2.0 mm and ≤ 4.0 mm.
8. Subject or legal representative is able and willing to give informed consent.

4.3.2. EXCLUSION CRITERIA

Subjects ***will not be eligible for the study*** if any of the following criteria are present:

1. The presence of an unsecured ruptured aneurysm. *Note unsecured unruptured aneurysms remote to the site of treated aSAH are not an exclusionary*.
2. Symptoms attributable to other causes (e.g., hydrocephalus, metabolic, infection).
3. Hunt and Hess Grade of 5
4. Large infarct on CT scan defined as ASPECTS 0-5.
5. Intracranial hemorrhage not caused by aneurysm rupture.
6. History of bleeding disorders.
7. Baseline platelets < 30,000
8. International normalized ratio (INR) > 1.7.
9. Any known contraindications to mechanical dilation of vasospastic vessels including but not limited to:

    - Excessive vessel tortuosity that prevents the placement of the device
    - Evidence of rapidly improving neurological signs of stroke

- Large territory completed cerebral infarction, edema with mass effect and intra-parenchymal hemorrhage in vascular territory to be treated, or
- any other vascular anatomic variants or anomalies

10. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. dementia with prescribed anti-cholinesterase inhibitor (e.g. Aricept).
11. History of severe allergy to contrast medium.
12. Known allergy to NeVa materials (nitinol, stainless steel).
13. Suspected or confirmed septic embolus, or bacterial endocarditis.
14. Septic shock or central nervous system (CNS) infection confirmed via cerebrospinal fluid (CSF) sampling.
15. Known current or recent use of illicit drugs or alcohol abuse.
16. Females who are pregnant or breastfeeding.
17. Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the subject if an endovascular procedure is performed.

4.4. STUDY PROCEDURES

Prior to recruitment of any subjects into the study, written approval of the protocol and informed consent must be obtained from the IRB.

4.4.1. INFORMED CONSENT

The investigator will explain the study purpose, procedures, and subject's responsibilities to the potential participant and/or legal representative. The subject's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained (Appendix 2). The subject or legal representative will sign and date the informed consent form. The investigator will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the subject or legal representative.

Following is a detailed list of study visits from screening to final follow-up and the required procedures/tests. Methodologies for specific tests/ procedures are described in Section 4.

4.4.2. SUBJECT IDENTIFICATION

To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form. A subject is considered enrolled after informed consent has been obtained. Each enrolled subject will be assigned a unique identifier in the following format: XX-YY-0. XX is the 2-digit assigned site number, YY is the 2-digit sequential subject ID number starting with 01, and "0" defines the initial treatment. If retreatment is needed, the subject is assigned the same site and subject number but now with treatment type "A" for the first retreatment, "B" for the second, etc. For example, the first treatment of the first subject at site 04 will be assigned 04-01-0; if this subject requires retreatment, the

subject ID will be 04-01-A. Subject ID numbers will not be re-used (e.g., if the subject is determined to be a screen failure).

4.4.3. SCREENING (DAY 0 TO DAY 21 POST aSAH)

Due to the emergent nature of vasospasm, all patients admitted with subarachnoid hemorrhage secondary to a ruptured aneurysm that was secured with surgical clipping or endovascular intervention with a Hunt and Hess Scale grade of 4 or less will proceed with screening.

Prior to screening, the subject/legal representative will provide informed consent. Screening should be completed between Day 0 to Day 21 following aSAH. Test results from routinely performed standard assessments may be used to determine eligibility including a DSA or CTA at time of aSAH presentation or aSAH intervention which must be available for review.

Screening to determine eligibility will be assessed sequentially, starting with the least invasive and least expensive tests as follows. ***Results from each test / screening activity should be reviewed prior to proceeding to the next step.***

- Evaluation of eligibility
- Medical history (including modified Fisher scale and Hunt-Hess grading at time of aSAH)
- Concomitant medications
- Vital signs
- Pre-hospital and current modified Rankin Scale (mRS)
- NIH Stroke Scale (NIHSS)
- Coagulation panel
- Urine pregnancy test (women of childbearing potential only), *Pregnancy test does not need to be repeated if obtained at current hospital admission.*
    - *Note, laboratory testing does not need to be repeated if testing was performed within the past 72 hours of the NeVa VS procedure and results are available.*
- Non-contrast head CT-scan to determine ICH.

Patients who subsequently experience vasospasm in the ICA, basilar, MCA, ACA or PCA territory on TCD and/or clinical signs of symptomatic vasospasm (change in level of consciousness, focal neurological deficit) will be eligible to participate in the study.

4.4.3.1. SCREEN FAILURES

Subjects not meeting all study entry criteria will be designated as screen failures. End of study procedures will not be performed for these subjects, but their reason for ineligibility will be recorded on the Screening Log. Screen failures are not counted towards total study enrollment.

4.4.4. DAY 0 – NEVA VS INTERVENTION

4.4.4.1. DIGITAL SUBTRACTION ANGIOGRAPHY (DSA)

DSA including AP and LAT views with late arterial phase in lateral view, will be obtained at the beginning of the intervention, and at the end of the procedure. Take all necessary precautions to limit X-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

The DSAimaging study will be reviewed and assessed by an independent core laboratory after the procedure.

4.4.4.2. ENDOVASCULAR TREATMENT

Administer intravenous sedation or general anesthesia, as appropriate, to ensure subject safety and comfort.

Systemic anticoagulation with heparin may be used during the procedure at the discretion of the neurointerventionist. Use of IV or IA antiplatelets is strongly discouraged.

The Neva VS device is a percutaneously introduced into the cerebral vasculature for the dilation of targeted spastic vessels with controlled expansive radial force. The Neva VS device will be navigated to the most distal size compatible (≥ 2.0mm and ≤ 4.0mm diameter on baseline DSA) location of the affected area. The Neva VS device will be deployed from distal location to proximal location by unsheathing, controlled dilation, and re-sheathing the device, retracting the microcatheter and unsheathing, dilation and re-sheathing more proximally until the entire affected vascular territory has been treated. Do not to advance or withdraw the device against resistance or significant vasospasm as moving or torqueing of the device against resistance or significant vasospasm may result in damage to the vessel or device.

A final DSA will be performed at the end of the procedure to characterize the degree of narrowing in the treated segment(s) of the target vessel. Procedural complications will be documented.

Vesalio acknowledges that it may be your practice and / or your institution's policy to use intra-arterial calcium channel blockers in treating patients that have experienced subarachnoid hemorrhage. We understand that this is done as a neuroprotective measure for these patients. This is consistent with and recommended by the American Heart Association as part of the standard of care. Please note, however, that this method and dose of administration has not been reviewed or approved by FDA for commercial use.

Do not proceed with use of the NeVa VS device if the primary vasospasm is resolved post-intra-arterial administration of calcium channel blockers. We urge you

to continue to follow and comply with your institution's policies and to document the type, time, dosage, and route of administration for this type of intervention (if used) in the Concomitant Medications form.

Use of any balloon angioplasty intervention as a rescue therapy is off-label and prohibited in this study.

4.4.5. 24 HRS ± 6 HOURS POST TREATMENT WITH NEVA VS

The following procedures will be performed:

- Vital signs
- Determine ICH as indicated by NCCT
- TCD
- NIHSS
- Concomitant medications
- AE assessment

4.4.6. DAY 21 ± 2 DAYS POST ASAH OR DISCHARGE (WHICHEVER OCCURS FIRST)

The following procedures will be performed on Day 21 post aSAH or at discharge (whichever occurs first):

- Determine ICH as indicated by NCCT
- TCD
- NIHSS
- mRS
- Concomitant medications
- AE assessment

4.4.7. DAY 30 ± 7 DAYS POST INITIAL TREATMENT WITH NEVA VS

- mRS
- AE assessment

4.4.8. ADDITIONAL TREATMENT OR RETREATMENT AFTER INITIAL INTERVENTION

If vasospasm recurs in a previously treated segment or in another (different) vessel / vessel segment or territory after treatment of the initial vasospasm but prior to hospital discharge, treatment with the NeVa VS is allowed if the subject still meets all study entry criteria. If a subject is retreated, he or she will be followed up for 30 more days per the retreatment schedule in Appendix 1. All treated areas will be imaged accordingly.

4.4.9. UNSCHEDULED VISITS

As clinically indicated, and corresponding data must be documented.

4.5. STUDY COMPLETION

4.5.1. COMPLETED SUBJECTS

Each subject in the study will be considered completed when all assessments through the Day 30 visit have been performed in accordance with the study protocol.

4.5.2. DISCONTINUED SUBJECTS

Any subject may voluntarily discontinue the study at any time without prejudice. The investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded.

Possible reasons for study discontinuation include the following:

- Adverse events (AEs) necessitating discontinuation from the study.
- Subject decision (specify).
- Investigator decision (specify).
- Other reason (specify).

The reasons for any subject discontinuation will be recorded on the study completion form of the study worksheets. If possible, subjects who withdraw prior to study completion will undergo the following:

- NIHSS
- mRS
- AE assessment

Lost to follow-up will only be considered at the 30-day visit. All other visits will be considered missed visits if the subject is unable to attend. Every attempt must be made to have subjects complete the study. The investigator/designee must do his/her best to contact the subject by phone at least twice, followed by a certified letter if unsuccessful. If no response is obtained from the subject, the investigator/designee is encouraged to contact one of the subject's relatives or his/her general practitioner. Documentation of these contacts must be recorded in the subject's source. In cases where the subject cannot be contacted by phone or letter, the site must attempt to review the death registry, if possible, and gather death certificates.

4.5.3. PREMATURE STUDY TERMINATION

The Sponsor reserves the right to discontinue the study for any safety, ethical or administrative reason at any time.

4.6. INVESTIGATIONAL DEVICE ACCOUNTABILITY

Documentation of receipt, use and return of all NeVa VS devices must be maintained by the Principal Investigator (PI) or his/her designee. Investigational NeVa VS devices are to be used only in accordance with this protocol and under supervision of the PI or a duly designated person. It is the PI's responsibility to ensure that all study devices are kept in a secure location, with access limited to individuals authorized by the investigator. A record of all study devices received, used and returned must be maintained by the site until the conclusion of the study. Following accountability of the study devices by the Sponsor or its designee, all unused study devices will be returned to the Sponsor/Designee as directed in writing by the Sponsor or designee for gross reconciliation.

4.7. CONCOMITANT MEDICATION

Systemic anticoagulation with heparin may be used during the procedure at the discretion of the neurointerventionist. Use of IV or IA antiplatelets is strongly discouraged. The use of oral antiplatelets as per local protocols is acceptable.

Subcutaneous low molecular weight (LMW) heparin is allowed for deep vein thrombosis (DVT) prophylaxis per the center's standard of care. Oral Nimodipine treatment (60mg PO Q6hours) starting at presentation through post aSAH day 21 is strongly encouraged except when contra-indicated.

Vesalio acknowledges that it may be your practice and / or your institution's policy to use intra-arterial calcium channel blockers in treating patients that have experienced subarachnoid hemorrhage. We understand that this is done as a neuroprotective measure for these patients. This is consistent with and recommended by the American Heart Association as part of the standard of care. Please note, however, that this method and dose of administration has not been reviewed or approved by FDA for commercial use. ***Do not proceed with use of the NeVa VS device if the primary vasospasm is resolved post-intra-arterial administration of calcium channel blockers.*** We urge you to continue to follow and comply with your institution's policies and to document the, type, time, dosage, and route of administration for this type of intervention (if used) in the Concomitant Medications form.

Concomitant medications will be recorded at Screening, 24 hours and Day 21 post aSAH or discharge (whichever occurs first). For each medication taken, the following information will be collected:

- Medication trade or generic name;
- Indication for which the medication was given;
- Dose/strength, route, and frequency of administration;
- Date started and date stopped (or continuation at Day 21 post SAH or discharge [whichever occurs first]).

5. EXAMINATIONS AND EVALUATIONS

5.1. EVALUATIONS CONDUCTED AT SCREENING ONLY

5.1.1. MEDICAL HISTORY

A medical history will be obtained at Screening. All positive and negative findings will be carefully documented on the study worksheets. Any new finding discovered during the Screening evaluation and prior to the index procedure will be considered to be part of the medical history and will not be recorded as an AE.

5.1.2. LABORATORY TESTING

Laboratory testing will be conducted by a local laboratory at each site at Screening. Laboratory testing does not need to be repeated if testing was performed within the past 72 hours and results are available. A coagulation panel including partial thromboplastin time (PTT), prothrombin time (PT) and international normalized ratio (INR) will be conducted.

5.1.3. PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL ONLY)

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be confirmed negative at time of current hospitalization or performed at Screening. Results of the test must be negative. Confirmed menopause is defined the absence of menses for at least 12 months prior to screening.

5.1.4. MODIFIED FISHER SCALE

The modified Fisher scale at the time of aSAH diagnosis will be recorded (Table 2).

Table 2. Modified Fisher Scale

Score	Description
0	No SAH, no intraventricular hemorrhage (IVH)
1	Focal or diffuse thin SAH, no IVH
2	Focal or diffuse thin SAH with IVH
3	Thick focal or diffuse SAH, no IVH
4	Thick focal or diffuse SAH with IVH

Note: thin SAH is 1 mm thick and thick SAH is ≥ 1mm in depth

5.1.5. HUNT-HESS GRADING SYSTEM

The Hunt-Hess grade at the time of aSAH diagnosis will be recorded (Table 3). Only patients with a Hunt and Hess Scale grade of 4 or less are eligible for study participation.

Table 3. Hunt Hess Grading System

Score	Description
0	Unruptured aneurysm
1	Asymptomatic or minimal headache and slight neck stiffness
2	Moderate to severe headache, neck stiffness, no neurological deficit except cranial nerve palsy
3	Drowsy, minimal neurologic deficits
4	Stuporous, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances
5	Deep coma, decerebrate rigidity, moribund appearance

5.2. EVALUATIONS CONDUCTED DURING THE STUDY

5.2.1. VITAL SIGNS

Vital signs consisting of blood pressure (supine), temperature, weight (at Screening only), heart rate, and respiratory rate will be recorded at Screening and 24 hours.

5.2.2. IMAGING TO DETERMINE INTRACRANIAL HEMORRHAGE

NCCT will be performed at Screening, 24 hours and Day 21 post aSAH or discharge to assess intracranial hemorrhage. The Alberta Stroke Program Early CT score (ASPECTS) will be determined. The ASPECTS score is a 10-point quantitative topographic CT scan score, determined from evaluation of two standardized regions of the MCA territory: the basal ganglia level, where the thalamus, basal ganglia, and caudate are visible, and the supraganglionic level, which includes the corona radiata and centrum semiovale. All cuts with basal ganglionic or supraganglionic structures visible are required to determine if an area is involved. The abnormality should be visible on at least two consecutive cuts to ensure that it is truly abnormal rather than a volume averaging effect. To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischemic change for each of the defined regions (Figure 12).

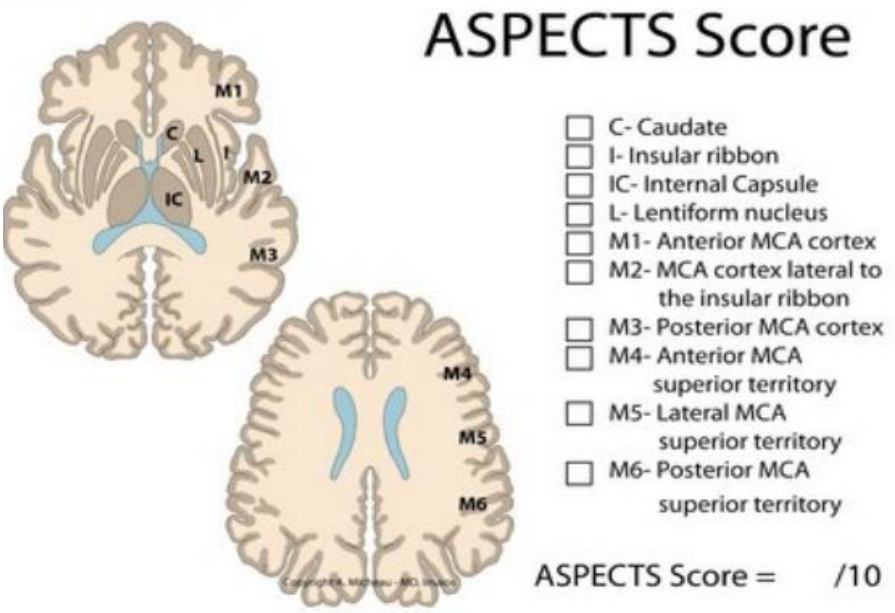


Figure 12.ASPECTS score

M4, M5, M6 are the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, rostral to basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5and M6. A normal CT scan receives ASPECTS of 10 points. A

score of 0 indicates diffuse involvement throughout the MCA territory. In order to be eligible for study participation, ASPECTS must be > 5 at Screening.

5.2.3. TRANSCRANIAL DOPPLER (TCD)

AHA/ASA guidelines indicate that it is reasonable to monitor for the development of arterial vasospasm following aSAH.[25] Transcranial Doppler provides a noninvasive method for recording blood flow velocity (and indirectly, diameter) in the basal cerebral arteries and therefore is especially useful in detecting vasospasm following subarachnoid hemorrhage. Vasospasm most commonly involves the basal arteries, where the changes in vessel diameter will be inversely proportional to the mean velocity measurements. Examination of patients requires that the examiner be experienced and familiar with the vascular anatomy and the various TCD indicators of vasospasm. For example, normal mean velocity for the MCA is 62 +/- 12 cm/sec. Significant spasm on angiogram of the MCA corresponds to a mean velocity of 120 cm/sec. Mean velocities of the MCA of 200 cm/sec or greater indicate severe spasm and correlate with 50% or greater narrowing on angiogram.[61]

It is expected that participating centers will monitor aSAH patients with TCD as part of standard of care. Patients with suspected vasospasm on TCD will be asked to participate in the study. Vasospasm of > 50% for study eligibility can only be confirmed by DSA. Following the index procedure, TCD will be performed at 24 hours and on the Day 21 post aSAH or discharge visit. TCD will not be assessed by the Core lab.

5.2.4. CT ANGIOGRAPHY

CT Angiography has been increasingly used as a noninvasive tool to diagnostic vasospasm with a relatively high degree of accuracy and may be used a study screening tool. However, for purposes of study eligibility, vasospasm of > 50% must be confirmed by DSA.

5.2.5. DIGITAL SUBTRACTION ANGIOGRAPHY (DSA)

DSA will be performed at Screening to determine the extent of stenosis in the ICA, basilar, MCA, ACA or PCA territories. Only subjects with > 50% in any of these territories will undergo the index procedure.

At the intervention, DSA including AP and LAT views with late arterial phase in lateral view, will be obtained at the beginning of the intervention, and at the end of the procedure and will be assessed by the treating interventionalist. The DSAimaging study will subsequently be reviewed and assessed by an independent core laboratory.

5.2.6. MODIFIED RANKIN SCALE (MRS)

The mRS is provided in Table 4. The mRS measures the degree of disability or dependence in daily activities.[62] At screening, a pre-hospital (historic) mRS and current mRS will be obtained by the site. At Day 21 post aSAH or discharge (whichever occurs first) and Day 30 visits, mRS will be determined.

Table 4. mRS

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

5.2.7. NIH Stroke Scale (NIHSS)

NIHSS (Appendix 4) is 15-item examination that measure stroke-related neurological deficits. Each specific ability is scored between a 0 and 4 (some elements have a scale from 0 to 2 or 0 to 3). For each item, a score of 0 typically indicates normal function, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a subject's total NIHSS score. NIHSS must be conducted by certified study personnel at Screening, 24 hours (+6/-6hours), and at Day 21 post aSAH or discharge (whichever occurs first). The interpretation of the NIHSS score is provided in Table 5.

Table 5. NIHSS

Score	Stroke Severity
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

5.2.8. Concomitant Medications

Concomitant medications will be documented at Screening, 24 hours and Day 21 days post aSAH or discharge (whichever occurs first) as described in Section 3.7.

6. Evaluation of Adverse Events

6.1. DEFINITIONS

An **adverse event (AE)** is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational medical device, whether or not considered causally related to the investigational medical device.

An untoward medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Conditions or diseases that are chronic but stable should not be recorded as an AE. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered AEs and should not be recorded on AE worksheets. These medical conditions should be adequately documented on the appropriate page of the study worksheet (relevant medical history). However, medical conditions present at enrollment that worsens in intensity or frequency in a manner inconsistent with the natural course of the disease during the treatment or post-treatment periods should be reported and recorded as AEs.

A **serious adverse event (SAE)** is any untoward medical occurrence which:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization (admission to hospital with a stay > 24 hours) or prolongation of hospitalization which is not specifically required by the protocol or is elective;
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Additionally, important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when they jeopardize the subject or require medical or surgical intervention to prevent one of the serious outcomes listed above.

An **unanticipated adverse device effect** (UADE) is defined as 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 predicate devices, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.2. ASSESSMENT OF ADVERSE EVENTS (AES)

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the study device or procedure. All AEs, regardless of

severity, occurring at Neva VS intervention through the Day 30 visit must be recorded. Events occurring prior to the endovascular (Neva VS) procedure must be listed in the medical history.

The following information should be obtained for each AE:

1. Event description. Every effort must be made to report the underlying condition or unifying diagnosis for the event. To avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words when possible. Signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the CRF (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

In addition, AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause (i.e., a "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record on AE CRF; events occurring secondary to the primary event should be described in the narrative description of the case [e.g., example: orthostatic hypotension → fainting and fall to floor → head trauma →neck pain; the primary AE is orthostatic hypotension]).

2. Duration: The date of onset and date of resolution should be reported. Every effort should be made to capture the exact dates.

3. Outcome: The final status of the event should be reported as resolved, ongoing, or if it resulted in death. If the event is present at the final study visit, the ongoing box must be marked.

4. Severity: The worst severity of the event must be reported as mild, moderate, or severe using the following definitions:

-Mild: Aware of sign or symptom, but easily tolerated
-Moderate: Discomfort enough to cause interference with usual activity
-Severe: Incapacitating with inability to work or do usual activity

5. Action taken: Treatment of the event may be reported as none, medical and/or surgical.

6. Seriousness: Determined by using the criteria in Section 5.1.

7. Relationship to device (study device or ancillary[i] device), and procedure/ treatment. The relationship to device and study procedure will be assessed using the following criteria.

[i] Ancillary device includes microcatheter, guide catheter, or another device that is not the study device (Neva VS device)

Definitely Not Related	Evidence exists that the adverse event definitely has a cause other than the device/procedure under investigation (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
Possibly Related	A temporal relationship exists between the event onset and the device/procedure under investigation. Although the adverse event may appear unlikely to be related to the device/procedure under investigation, it cannot be ruled out with certainty; and/or the event cannot be readily explained by the subject's clinical state or concomitant therapies.
Definitely Related	Strong evidence exists that the device/procedure under investigation caused the adverse event. There is a temporal relationship between the event onset and the device/procedure under investigation. There is strong therapeutic evidence that the event was caused by the device/procedure under investigation. The subject's clinical state and concomitant therapies have been ruled out as a cause.
Unknown	Unable to make a determination on causality of the event.

6.3. REPORTING/RECORDING OF AES

Throughout the course of the study, all efforts will be made by the investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and for providing appropriate medical intervention. The period of observation for collection of AEs starts at index (Neva VS) procedure until the Day 30 follow-up visit. Any AE should be recorded on the appropriate study worksheet.

6.4. SAES REQUIRING EXPEDITED REPORTING

Serious adverse events (SAEs) that occur within 24 hours of the NeVa VS intervention require expedited reporting to the Sponsor or designee regardless of relationship to study device or study procedure. In addition, UADEs require expedited reporting.

All SAEs that occur within 24 hours of the index procedure, including death, and suspected UADEs must be reported within 3 working days to the study Sponsor/Designee, by:

- **Completing the AE information in the Electronic Data Capture (EDC) system and selecting appropriate criteria that classifies the AE as serious.**
- **Completing and uploading the SAE form in the EDC.**

In order to have the Investigator's signature on file, the signed SAE form needs to be uploaded to the EDC at the time of initial data entry.

In case of death, the site will provide a copy of the death certificate and autopsy report, if applicable, to the Sponsor/Designee. If no such documents are available,

the Investigator will describe the circumstances of the subject's death in the source document.

The investigator must follow their local IRB policy for SAE reporting.

The Sponsor/Designee will review all SAEs and suspected UADEs and determine if the SAE constitutes a UADE. All UADEs will be reported to all reviewing IRBs and participating investigators within 10 days after the Sponsor first receives notice of the effect.

6.5. ANTICIPATED COMPLICATIONS/AES

Anticipated complications/AEs are defined as complications/events that can be reasonably associated with aSAH or the use of the Neva VS device.

Potential procedural complications include, but are not limited to:

- Hematoma and hemorrhage at the puncture site
- Perforation or dissection of the vessel
- Vasoconstriction (vasospasm)
- Change in mental status
- COMA/Persistent Vegetative State
- Persistent neurological deficits
- Neurological deterioration including stroke progression, stroke in a new vascular territory and death
- Transient ischemic attack
- Brain edema
- Ischemia
- Infection
- Allergic reaction/adverse reaction to device materials, procedure medications or contrast media
- Air embolism
- Intracranial hemorrhage
- Vascular occlusion
- Pseudoaneurysm formation
- Post procedural bleeding
- Peripheral nerve damage (e.g., femoral nerve)
- Distal embolization including to a previously uninvolved territory
- Device(s) deformation, collapse, fracture or malfunction
- Thrombosis (acute and subacute0
- Arteriovenous fistula
- General discomfort, tenderness, pain
- Nausea and/or vomiting
- Radiation effects, including, but not limited to: alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia

- Death

Anticipated AEs include, but are not limited to:

- Blood and lymphatic system disorders
  - Anemia
  - Thrombocytopenia
- Cardiac disorders
  - Atrial fibrillation
  - Bradycardia
  - Cardiac arrest
  - Congestive heart failure
  - Tachycardia
- Death
- Eye disorders
  - Retinal artery embolism
- Gastrointestinal disorders
  - Abdominal pain
  - Dysphagia
  - Gastrointestinal hemorrhage
  - Hematochezia
  - Nausea
  - Upper gastrointestinal hemorrhage
  - Vomiting
- General disorders
  - Catheter site hematoma
  - Pyrexia
- Infections and Infestations
  - Bacteremia
  - Clostridia infection
  - Pneumonia
  - Sepsis
  - Urinary tract infection
- Injury, poisoning and procedural complications
  - Traumatic pneumothorax
  - Vascular access complication
- Investigations
  - Abnormal echocardiogram
  - Increased international normalized ratio
- Metabolism and nutrition disorders
  - Diabetes
  - Electrolyte imbalance
  - Hyperglycemia
  - Hypoglycemia
  - Hypokalemia
- Musculoskeletal and connective tissue disorders
  - Compartment syndrome

    - Musculoskeletal pain
- Nervous system disorders
    - Brain edema
    - Carotid artery dissection
    - Cerebral gas embolism
    - Cerebral hematoma
    - Cerebrovascular accident
    - Cerebrovascular spasm
    - Clonus
    - COMA
    - Convulsion
    - Depressed level of consciousness
    - Hemorrhagic cerebral infarction
    - Headache
    - Increased intracranial pressure
    - Intraventricular hemorrhage
    - Ischemic stroke
    - Persistent Vegetative State
    - Subarachnoid hemorrhage
- Psychiatric disorder
    - Agitation
- Respiratory and thoracic mediastinal disorders
    - Atelectasis
    - Dyspnea
    - Hypoxia
    - Pleural effusion
    - Pneumonia aspiration
    - Pneumothorax
    - Pulmonary edema
    - Respiratory distress
    - Respiratory failure
    - Vascular disorders
- Vascular disorders
    - Deep vein thrombosis
    - Hypertension
    - Hypotension
    - Vasospasm
    - Vessel perforation

6.6. DEVICE MALFUNCTION

Device malfunction is defined as failure of the device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use (IFU) or clinical investigational plan.

Device failure may or may not result in an AE/SAE. All AEs/SAEs associated with a device failure are by definition device-related.

7. STATISTICAL METHODS

The primary goal of this study is to assess the safety and probable benefit of the Neva VS device in patients presenting with symptomatic cerebral vasospasm despite maximal medical management following aSAH. Sample size estimations were not based on formal statistical hypotheses testing because the patent population and annual incidence of symptomatic cerebral vasospasm after aSAH is less than 8000 cases / year. Hypothesis testing will not be performed on any endpoint.

7.1. PATIENT CATEGORIZATION

Screen Failure - Any patient who was consented and entered into the screening process appropriately, but subsequently did not meet the entry criteria in order to be treated. Patients who fail screening will not be followed for safety or feasibility assessment, and no other study procedures will be performed.

Evaluable Patient - Any patient who in whom the Neva VS procedure was started, defined as introduction of a Neva VS device into the vasculature (regardless of the ability to reach the target vessel.

Lost to follow-up - A patient deemed to be lost to follow-up is any patient who underwent the Neva VS procedure, but who does not complete scheduled study visits. This includes those patients who withdraw consent and refuse further study participation and all attempts to contact the patient are deemed unsuccessful.

7.2. STUDY OUTCOMES

The following study outcomes will be determined in evaluable patients:

- ***Procedural Success*** - defined as 50% or greater vessel caliber on DSA compared to baseline, as determined by the core laboratory.
- ***Retreatment / additional treatment*** – the rate of retreatment or treatment of additional territories will be quantified.
- ***Symptomatic Improvement*** - for clinically symptomatic patients, a decrease at 24 hours of ≥ 3-points from Screening as measured by NIHSS and/or resolution of pre-procedural clinical deficits.
- ***Change in ASPECT Score*** –change in ASPECT score on NCCT from Screening to Day 21 or discharge, whichever occurs first
- ***Clinical Status*** – Change in modified Rankin Scale score from Screening at Day 30

7.3. SAFETY

All evaluable patients will be included in the safety analyses. Adverse events and serious adverse events will be summarized using descriptive statistics.

7.4. STATISTICAL ANALYSES

Descriptive statistics will be performed. Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using n, mean, SD, median, minimum, and maximum values. No statistical testing will be performed.

8. IMAGING CORE LABORATORY

The goal of the core lab is to provide unbiased assessment of DSA/CTA imaging obtained at the time of aSAH presentation or intervention and DSA obtained during the Neva VS procedure. Specifically, DSA including AP and LAT views with late arterial phase in lateral view, will be obtained at the beginning of the intervention with the Neva VS device, and at the end of the procedure. These images will be sent to the core laboratory post-procedure.

The imaging procedures will be defined in the Core Lab Manual. De-identified images will be sent directly from the site to the core lab.

9. DATA SAFETY MONITORING BOARD (DSMB)

The independent data safety monitoring board (DSMB) will periodically review a limited set of tables and/or listings, including all reported SAEs. The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to Sponsor regarding the safety of the NeVa VS system. There will be no adjustment for multiple testing due to the DSMB data review. Further details of DSMB responsibilities are included in the DSMB Charter.

10. ACCESS TO STUDY DOCUMENTS AND STUDY MONITORING

The Sponsor has designated BioMDG to monitor the progress of this study. The clinical monitor, as a representative of the Sponsor, has the obligation to follow this study closely.

The Sponsor or its designee may meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.

During the study, the clinical monitor will visit the study facilities regularly, and utilize telephone and written communications on an ongoing basis to maintain current knowledge of the study. During periodic visits to the study site, the monitor will review the source documents used for data entry in the EDC system to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. Source documents must contain all data entered in the EDC system. All data generated during this study and the source documents from which they originated are subject to inspection by the Sponsor or its representatives, the FDA and other regulatory agencies.

Upon completion of the study, the clinical monitor will conduct a final visit (close-out) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that study drug and other supplies have been accounted for and ensure that the investigator is aware of his/her responsibilities post-study.

11. QUALITY CONTROL AND ASSURANCE

The Sponsor and/or its contracted representatives utilize Standard Operating Procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and Good Clinical Practice guidance.

A quality assurance audit may be conducted by the Sponsor or its designee at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to, a review of all informed consent forms, source documents, medical records, regulatory documentation, an assessment of study conduct and protocol compliance, and a review of the investigational drug accountability. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the findings of the audit.

11.1. TRAINING

Each site will be trained to the investigational plan prior to performing any study-related procedures. Procedure training will be completed by an experienced Procedural/Clinical Specialist in both a classroom and simulated environment and may include use of an in-vitro or in-vivo model.

12. INSTITUTIONAL REVIEW BOARD (IRB)

Prior to the initiation of the study, the protocol, and the informed consent form will be submitted to the IRB for approval. By signing the clinical trial agreement, the investigator

is assuring that an IRB which complies with the requirements set forth in 21 CFR Part 56, will be responsible for the initial and continuing review of the proposed clinical study. A copy of the IRB approval letter for the protocol, the informed consent, and the protocol signature page must be submitted to the Sponsor or its designee, prior to release of investigational supplies to the study site. The approval letter must refer to the specific protocol and the informed consent form. The study site must maintain an accurate and complete record of all reports, documents and other submissions made to the IRB concerning this protocol. A list of the IRB members, their titles or occupations, and their institutional affiliation, or an IRB assurance number must be provided to the Sponsor or its designee prior to release of study supplies.

The investigator is responsible for notifying the IRB of any SAEs and UADE as required by the IRB. A copy of the notification must be forwarded to BioMDG.

Status reports must be submitted to the IRB at least once a year (or more frequently as required by the IRB) and the IRB must be notified of completion or termination of the study. A final report must be provided to the IRB and the Sponsor within 2 months of study completion or termination. This report should include: any deviations from the protocol, the number of participants evaluated, the number of participants who withdrew or were withdrawn and the reasons for withdrawal, any significant AEs and the investigator's summation of the study.

13. INFORMED CONSENT PROCESS

It is the responsibility of the investigator to inform each subject or his/her legal representative, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. A sample informed consent form containing the required elements of informed consent is provided in Appendix 2. Any changes made to this sample must be approved by the Sponsor or its designee, prior to submission to an IRB. After approval by the Sponsor or its designee, the informed consent must be submitted to and approved by an IRB. Prior to entry into the study or initiation of any study-related procedures, the subject or his/her legal representative must read, sign and date the informed consent form. The person executing the consent must also sign and date the IRB-approved consent form. One original informed consent form is to be retained by the study site and a copy is to be given to the subject or his/her legal representative. The informed consent process must be documented in the subject's source/medical record.

The informed consent must be written in a language in which the subject or his/her legal representative is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The investigator must forward a copy of the consent form, the certified foreign language translation and an IRB approval letter to the Sponsor or its designee.

14. CONFIDENTIALITY

In accordance with GCP and with the national data protection laws, all information concerning the subjects in the study must be treated as strictly confidential by all persons involved in the study.

The investigator acknowledges that all information acquired from the Sponsor or its designee or developed or acquired in connection with the study are strictly confidential. The investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Sponsor in writing. Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

15. PROTOCOL AMENDMENTS

The Sponsor will document modifications to the protocol in the form of a written amendment. Protocol modifications that impact subject safety or the validity of the study must be approved by the IRB before implementation. In the case of a medical emergency, to remove immediate apparent hazard to subjects, a change may be made preferably after discussion with the Sponsor or its designee. In these instances, the IRB and FDA will be notified as soon as possible.

16. DATA MANAGEMENT

Electronic data capture (EDC) will be utilized for this study. Study worksheets will be provided by the Sponsor or its designee to the site before data collection. To facilitate data entry, the worksheets will coincide with the data entry pages in the EDC system to insure minimal issues during data entry. If the site elects to use the worksheets, appropriate worksheets will be completed and initialed or signed where indicated at each examination. All worksheets will be completed in a legible manner in black/blue ink. Alternatively, the site may elect to use their own source documents. It is expected that there will be source data for all entries in the EDC.

Any corrections to the worksheets will be made by drawing a single line through the incorrect entry, recording the correct information, and initialing and dating the change. The study worksheets and data entered in the EDC system will be audited by the Study Monitor.

Once the data is ready to be entered into the EDC System, then the site will begin entering the data into the system. The monitor will review data entered into the EDC against the source documents and/or worksheets and either approve the data records or create queries

to the site for further review. If the data records are deemed "clean" with the approval of the monitor, then the investigator can e-sign the records. Finally, when the data records are ready to be locked, the data manager will perform the interim lock in the system. However, the data manager also has the right to unlock the data record if any updates to the data are necessary.

Data are protected by preventing unauthorized users from accessing the system with the use of username and password combination. In addition, each individual user will be assigned a specific role in the EDC System which will grant that user the right to enter, view, edit and/or delete the data. Furthermore, any changes to the data are captured in the EDC System's audit trail where a reason for change is required.

All clinical data generated in the study will be submitted to the Sponsor or designated CRO for quality assurance review and statistical analysis. All worksheets and data entered into the EDC system will be reviewed for completeness and evident recording errors will be rectified by contact with the appropriate clinical site. Computerized data checks will be used to identify unusual data entries for verification prior to statistical analysis.

To minimize the amount of missing data, investigators will be trained on the deleterious effect that missing data have on trial integrity and credibility and that missing data could diminish the scientific value of all subjects' altruistic contributions.

17. RECORD KEEPING AND RETENTION

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor and its representatives and FDA/relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality.

An investigator must in reasonable time, upon request from any properly authorized officer or employee of FDA/relevant health authority or regulatory agency, permit such officer or employee to have access to requested records and reports, and copy and verify any records or reports made by the investigator. Upon notification of a visit by the FDA/relevant health authority or regulatory agency, the investigator will contact the Sponsor or its designee immediately. The investigator will also grant Sponsor representatives the same privileges offered to FDA/relevant health authority or regulatory agents/officers/employees.

The Investigator must provide the Sponsor/Designee with the following documents prior to study initiation and retain a copy in the study file:

- Current signed curriculum vitae (within 2 years prior to study initiation) and current medical licenses for the Principal Investigator and all co-investigators listed on the clinical trial agreement.

- A copy of the original approval for conducting the study by the IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy.
- A copy of the IRB approved informed consent form.
- IRB member list and/or DHHS General Assurance Number (if IRB has an Assurance number).
- Signed Financial Disclosure Form for the Principal Investigator and all co-investigators listed on the clinical trial agreement,
- The signature page of this protocol signed and dated by the Principal Investigator.

In addition to the documents listed above, the study site will also retain the following items:

- Certifications and laboratory reference ranges for all local laboratories used for this study.
- Delegation of authority log.
- All original informed consent forms with required signatures.
- All IRB correspondence.
- Study monitoring log.
- Screening/enrollment log.
- Device accountability records.
- Copies of all pertinent correspondence pertaining to the study (except budget issues) between the Sponsor or the CRO and the site.
- Copies of all SAEs forms/supporting documentation submitted to the Sponsor or its designee.

All study-related records must be maintained for at least 5 years after study completion. The Sponsor will notify the principal investigator when records are no longer needed. The investigator will not discard any records without notifying the Sponsor. If the principal investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

18. INVESTIGATOR FINAL REPORT

The investigator shall provide the IRB and the Sponsor with an accurate final report within 2 months after completion, termination or discontinuation of the study. The final report may not precede final data submission which has not been monitored.

19. STUDY REPORT AND PUBLICATION

The data resulting from this study will be the proprietary information of the Sponsor and may be made public after all data have been analyzed and the study results are available. None of the data resulting from this study will be allowed to be presented or published in any form, by the investigator or any other person, without the prior written approval of the Sponsor. At the end of the study, a clinical study report will be written by the Sponsor or its designee.

20. REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146-e603.
2. Venti M. Subarachnoid and intraventricular hemorrhage. Front Neurol Neurosci 2012;30:149-53.
3. Fotakopoulos G, Tsianaka E, Fountas K, Makris D, Spyrou M, Hernesniemi J. Clipping Versus Coiling in Anterior Circulation Ruptured Intracranial Aneurysms: A Meta-Analysis. World Neurosurg 2017;104:482-8.
4. le Roux AA, Wallace MC. Outcome and cost of aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am 2010;21:235-46.
5. Sanelli PC, Ugorec I, Johnson CE, et al. Using quantitative CT perfusion for evaluation of delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradiol 2011;32:2047-53.
6. Brown RJ, Kumar A, Dhar R, Sampson TR, Diringer MN. The relationship between delayed infarcts and angiographic vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery 2013;72:702-7; discussion 7-8.
7. Gross BA, Rosalind Lai PM, Frerichs KU, Du R. Treatment modality and vasospasm after aneurysmal subarachnoid hemorrhage. World Neurosurg 2014;82:e725-30.
8. Killeen RP, Gupta A, Delaney H, et al. Appropriate use of CT perfusion following aneurysmal subarachnoid hemorrhage: a Bayesian analysis approach. AJNR Am J Neuroradiol 2014;35:459-65.
9. Frontera JA, Fernandez A, Schmidt JM, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? Stroke 2009;40:1963-8.
10. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery 2006;59:21-7; discussion -7.
11. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. Nat Rev Neurol 2014;10:44-58.
12. Platz J, Guresir E, Wagner M, Seifert V, Konczalla J. Increased risk of delayed cerebral ischemia in subarachnoid hemorrhage patients with additional intracerebral hematoma. J Neurosurg 2017;126:504-10.
13. Feng H, Ying M, Zhang JH. Early brain injury or cerebral vasospasm. Wien ; New York: Springer; 2011.
14. Crobeddu E, Mittal MK, Dupont S, Wijdicks EF, Lanzino G, Rabinstein AA. Predicting the lack of development of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Stroke 2012;43:697-701.
15. Aldakkan A, Mansouri A, Jaja BN, Alotaibi NM, Macdonald RL, Subarachnoid Hemorrhage International Trialists C. Predictors of Delayed Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage with Asymptomatic Angiographic Vasospasm on Admission. World Neurosurg 2017;97:199-204.
16. Vergouwen MD, Vermeulen M, van Gijn J, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke 2010;41:2391-5.
17. Chang TR, Kowalski RG, Carhuapoma JR, Tamargo RJ, Naval NS. Impact of case volume on aneurysmal subarachnoid hemorrhage outcomes. J Crit Care 2015;30:469-72.
18. Leijenaar JF, Dorhout Mees SM, Algra A, van den Bergh WM, Rinkel GJ, Group M-IS. Effect of magnesium treatment and glucose levels on delayed cerebral ischemia in patients with

subarachnoid hemorrhage: a substudy of the Magnesium in Aneurysmal Subarachnoid Haemorrhage trial (MASH-II). Int J Stroke 2015;10 Suppl A100:108-12.
19. Mir DI, Gupta A, Dunning A, et al. CT perfusion for detection of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2014;35:866-71.
20. Stienen MN, Smoll NR, Weisshaupt R, et al. Delayed cerebral ischemia predicts neurocognitive impairment following aneurysmal subarachnoid hemorrhage. World Neurosurg 2014;82:e599-605.
21. Da Silva IR, Gomes JA, Wachsman A, de Freitas GR, Provencio JJ. Hematologic counts as predictors of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Crit Care 2017;37:126-9.
22. Thelin EP, Tajsic T, Zeiler FA, et al. Monitoring the Neuroinflammatory Response Following Acute Brain Injury. Frontiers in Neurology 2017;8:351.
23. Chen S, Feng H, Sherchan P, et al. Controversies and evolving new mechanisms in subarachnoid hemorrhage. Prog Neurobiol 2014;115:64-91.
24. Bederson JB, Connolly ES, Jr., Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009;40:994-1025.
25. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke 2012;43:1711-37.
26. Rahme R, Jimenez L, Pyne-Geithman GJ, et al. Endovascular management of posthemorrhagic cerebral vasospasm: indications, technical nuances, and results. Acta Neurochir Suppl 2013;115:107-12.
27. Iqbal S, Hayman EG, Hong C, et al. Inducible nitric oxide synthase (NOS-2) in subarachnoid hemorrhage: Regulatory mechanisms and therapeutic implications. Brain Circ 2016;2:8-19.
28. Pluta RM. Delayed cerebral vasospasm and nitric oxide: review, new hypothesis, and proposed treatment. Pharmacol Ther 2005;105:23-56.
29. Siuta M, Zuckerman SL, Mocco J. Nitric oxide in cerebral vasospasm: theories, measurement, and treatment. Neurol Res Int 2013;2013:972417.
30. Findlay JM, Nisar J, Darsaut T. Cerebral Vasospasm: A Review. Can J Neurol Sci 2016;43:15-32.
31. Loch Macdonald R. Management of cerebral vasospasm. Neurosurg Rev 2006;29:179-93.
32. Phan K, Moore JM, Griessenauer CJ, et al. Ultra-Early Angiographic Vasospasm After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. World Neurosurg 2017;102:632-8 e1.
33. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 1989;298:636-42.
34. Kumar G, Shahripour RB, Harrigan MR. Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg 2016;124:1257-64.

35. Sarrafzadeh AS, Vajkoczy P, Bijlenga P, Schaller K. Monitoring in Neurointensive Care - The Challenge to Detect Delayed Cerebral Ischemia in High-Grade Aneurysmal SAH. Front Neurol 2014;5:134.
36. Inagawa T. Risk Factors for Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage: A Review of the Literature. World Neurosurg 2016;85:56-76.
37. Dabus G, Nogueira RG. Current options for the management of aneurysmal subarachnoid hemorrhage-induced cerebral vasospasm: a comprehensive review of the literature. Interv Neurol 2013;2:30-51.
38. Biondi A, Ricciardi GK, Puybasset L, et al. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. AJNR Am J Neuroradiol 2004;25:1067-76.
39. Hockel K, Diedler J, Steiner J, Birkenhauer U, Ernemann U, Schuhmann MU. Effect of Intra-Arterial and Intravenous Nimodipine Therapy of Cerebral Vasospasm After Subarachnoid Hemorrhage on Cerebrovascular Reactivity and Oxygenation. World Neurosurg 2017;101:372-8.
40. Bashir A, Andresen M, Bartek J, Jr., Cortsen M, Eskesen V, Wagner A. Intra-arterial nimodipine for cerebral vasospasm after subarachnoid haemorrhage: Influence on clinical course and predictors of clinical outcome. Neuroradiol J 2016;29:72-81.
41. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care 2011;15:211-40.
42. Maher M, Schweizer TA, Macdonald RL. Treatment of Spontaneous Subarachnoid Hemorrhage: Guidelines and Gaps. Stroke 2020;51:1326-32.
43. Connolly Jr ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;43:1711-37.
44. Zwienenberg-Lee M, Hartman J, Rudisill N, et al. Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial. Stroke 2008;39:1759-65.
45. Patel AS, Griessenauer CJ, Gupta R, et al. Safety and Efficacy of Noncompliant Balloon Angioplasty for the Treatment of Subarachnoid Hemorrhage-Induced Vasospasm: A Multicenter Study. World Neurosurg 2017;98:189-97.
46. Heit JJ, Choudhri O, Marks MP, Dodd RL, Do HM. Cerebral angioplasty using the Scepter XC dual lumen balloon for the treatment of vasospasm following intracranial aneurysm rupture. J Neurointerv Surg 2015;7:56-61.
47. Roos YB, Dijkgraaf MG, Albrecht KW, et al. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. Stroke 2002;33:1595-9.
48. Elliott JP, Newell DW, Lam DJ, et al. Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 1998;88:277-84.
49. Muizelaar JP, Zwienenberg M, Rudisill NA, Hecht ST. The prophylactic use of transluminal balloon angioplasty in patients with Fisher Grade 3 subarachnoid hemorrhage: a pilot study. J Neurosurg 1999;91:51-8.

50. Higashida RT, Halbach VV, Dowd CF, Dormandy B, Bell J, Hieshima GB. Intravascular balloon dilatation therapy for intracranial arterial vasospasm: patient selection, technique, and clinical results. Neurosurg Rev 1992;15:89-95.
51. Hoh BL, Ogilvy CS. Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, and intra-arterial nicardipine. Neurosurg Clin N Am 2005;16:501-16, vi.
52. Mortimer AM, Steinfort B, Faulder K, et al. Institution of sustained endovascular treatment prior to clinical deterioration in patients with severe angiographic vasospasm: A retrospective observational study of clinico-radiological outcomes. J Neuroradiol 2015;42:176-83.
53. Chaudhry NS, Orning JL, Shakur SF, et al. Safety and efficacy of balloon angioplasty of the anterior cerebral artery for vasospasm treatment after subarachnoid hemorrhage. Interv Neuroradiol 2017;23:372-7.
54. Zubkov YN, Nikiforov BM, Shustin VA. Balloon catheter technique for dilatation of constricted cerebral arteries after aneurysmal SAH. Acta Neurochir (Wien) 1984;70:65-79.
55. Consigny PM, Tulenko TN, Nicosia RF. Immediate and long-term effects of angioplasty-balloon dilation on normal rabbit iliac artery. Arteriosclerosis 1986;6:265-76.
56. Yamamoto Y, Smith RR, Bernanke DH. Mechanism of action of balloon angioplasty in cerebral vasospasm. Neurosurgery 1992;30:1-5; discussion -6.
57. Grande A, Nichols C, Khan U, et al. Treatment of post-hemorrhagic cerebral vasospasm: role of endovascular therapy. Acta Neurochir Suppl 2011;110:127-32.
58. Chan PD, Findlay JM, Vollrath B, et al. Pharmacological and morphological effects of in vitro transluminal balloon angioplasty on normal and vasospastic canine basilar arteries. J Neurosurg 1995;83:522-30.
59. Linskey ME, Horton JA, Rao GR, Yonas H. Fatal rupture of the intracranial carotid artery during transluminal angioplasty for vasospasm induced by subarachnoid hemorrhage. Case report. J Neurosurg 1991;74:985-90.
60. Bhogal P, Loh Y, Brouwer P, Andersson T, Soderman M. Treatment of cerebral vasospasm with self-expandable retrievable stents: proof of concept. J Neurointerv Surg 2017;9:52-9.
61. Newell DW, Winn HR. Transcranial Doppler in cerebral vasospasm. Neurosurg Clin N Am 1990;1:319-28.
62. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.

APPENDICES

TABLE OF APPENDICES

Appendix 1. Schedule of Evaluations and Visits

SCHEDULE OF EVALUATIONS AND VISITS – INITIAL INTERVENTION

PROCEDURE	SCREENING (DAY 0-21 POST aSAH)	INTERVENTION DAY 0 (WITHIN 21 DAYS POST aSAH)[f]	24 HRS ± 6 HRS (POST DAY 0)	DAY 21 ± 2 DAYS POST aSAH OR DISCHARGE (WHICHEVER OCCURS FIRST)	DAY 30 ± 7 DAYS (POST DAY 0)	EARLY WITHDRAWAL
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Baseline Evaluations						
Informed Consent	✓					
Medical History	✓					
Modified Fisher scale [a]	✓					
Hunt-Hess grading system [a]	✓					
Coagulation panel	✓					
Urine pregnancy test (women of childbearing potential only)	✓					
Feasibility and Safety Parameters						
Vital signs	✓		✓			
Imaging to determine ICH, non-contrast head CT scan (NCCT)	✓		✓	✓		
Presentation of vasospasm [b]	✓					
Transcranial Doppler (TCD), and/or CT angiography	✓		✓	✓		
Confirmation of vasospasm DSA[c]	✓	✓				
Procedural success [d]		✓				
NIHSS	✓		✓	✓		✓
Modified Rankin Scale (mRS)	✓ [e]			✓	✓	✓
Concomitant Medications	✓	✓	✓	✓		
Adverse Events		✓	✓	✓	✓	✓

a. At the time of aSAH diagnosis
b. Documentation of vasospasm on TCD and/or clinical presentation
c. Vasospasm confirmed by DSA (greater than 50% stenosis in the ICA, Basilar, MCA, ACA or PCA territory)
d. Procedural success is defined as a reduction in vessel narrowing of 50% or greater in the treated segment when compared to baseline DSA or CTA.
e. Pre-hospital and current mRS
f. If another (different) vessel / territory experiences vasospasm after treatment of the initial vasospasm but prior to hospital discharge, treatment with the NeVa VS is allowed if the subject still meets all study entry criteria. See Schedule of Evaluations and Visits – Repeat Intervention. All treated areas will be imaged accordingly.

SCHEDULE OF EVALUATIONS AND VISITS – REPEAT INTERVENTION

PROCEDURE	SCREENING (DAY 0-21 POST aSAH)	INTERVENTION DAY 0 (WITHIN 21 DAYS POST aSAH)[f]	24 HRS ± 6 HRS (POST DAY 0)	DAY 21 ± 2 DAYS POST aSAH OR DISCHARGE (WHICHEVER OCCURS FIRST)	DAY 30 ± 7 DAYS (POST DAY 0)	EARLY WITHDRAWAL
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Feasibility and Safety Parameters						
Vital signs	✓		✓			
Coagulation panel	✓					
Eligibility determination	✓					
Imaging to determine ICH, non-contrast head CT scan (NCCT)			✓	✓		
Presentation of vasospasm [a]	✓					
Transcranial Doppler (TCD), and/or CT angiography	✓		✓	✓		
Confirmation of vasospasm DSA[b]		✓				
Procedural success [c]		✓				
NIHSS	✓		✓	✓		✓
Modified Rankin Scale (mRS)				✓	✓	✓
Concomitant Medications	✓	✓	✓	✓		
Adverse Events	✓	✓	✓	✓	✓	✓

a. Documentation of vasospasm on TCD and/or clinical presentation
b. Vasospasm confirmed by DSA (greater than 50% stenosis in the ICA, Basilar, MCA, ACA or PCA territory)
c. Procedural success is defined as a reduction in vessel narrowing of 50% or greater in the treated segment when compared to baseline DSA or CTA.

Appendix 2. Sample Informed Consent

SAMPLE SUBJECT INFORMATION SHEET / INFORMED CONSENT FORM / HIPAA AUTHORIZATION

TITLE:	The Vesalio™ Neva VS for the Treatment of Symptomatic Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage (aSAH) (The VITAL Study)
PROTOCOL NO.:	VS-002
SPONSOR:	Vesalio
INVESTIGATOR:	Name Address City, State Zip Country
SITE(S):	Name Address City, State Zip Country
STUDY RELATED PHONE NUMBER(S):	Name Phone number(s)
Subject Initials:	[_____]
Subject Number:	[_____]

WHY AM I BEING ASKED TO VOLUNTEER?

You are being asked to participate in a research study sponsored by Vesalio. Before you decide whether to participate, it is important for you to know why the research is being done, and what it will involve. Please take your time to read the following information carefully, and feel free to discuss your decision with your family, friends, and your primary care doctor. Please ask your study doctor to explain if there is anything that is not clear or if you would like more information. If you agree to take part in this study, you need to sign this consent form. Your signature on this form means that you have been told about and understand the purpose of the study, procedures to be followed, and any benefits or risks. Your signature on this form also means that you want to take part in this study if you meet the criteria, based on the results of

your medical tests, which must be done before you are asked to continue your participation in the study. After you agree, you will be provided with a copy of this signed form for your records.

DO I HAVE TO TAKE PART?
Taking part in this study is entirely voluntary, and you may refuse to participate or withdraw from the study at any time without influencing your regular medical treatment and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Regardless of your decision, you will still be treated for your medical condition.

WHY IS THE PURPOSE OF THIS?
The purpose of this research study is to find out if a medical device, the NeVa VS device, is able to treat vasospasms (abnormal narrowing of blood vessels in your brain) that developed after you experienced a subarachnoid hemorrhage (bleeding into the space surrounding your brain) caused by a ruptured aneurysm (large bulge of the blood vessel wall caused by weakening of the blood vessel wall) – hereinafter referred to as aneurysmal subarachnoid hemorrhage (aSAH).

This study is designed to assess the safety and probable benefit of using the Neva VS device. The Neva VS device is an investigational (experimental) device which means that the Neva VS device has not been approved by the US Food and Drug Administration (FDA).

WHO IS IN CHARGE OF THIS STUDY?
This study is sponsored and funded by Vesalio Co., Ltd. The Principal Investigator is being paid by Vesalio Co., Ltd. to conduct this study. Together with your doctor, Vesalio Co., Ltd. will also use a specialized research company, called a contract research organization, in addition to a specialized laboratory to manage some of the requirements of the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS RESEARCH STUDY?
Up to 150 patients will take part in this study at up to 15 hospitals.

WHAT HAPPENS IF I AGREE TO BE IN THIS RESEARCH STUDY?
After you sign this consent form indicating you want to participate in this study, you will need to undergo some tests to see if you qualify for the study. If you do not meet all of the study entry criteria, you will not be able to participate in the study and your study doctor will discuss with you other options that you may have for treatment of your medical condition.

This study is a prospective, open-label, single-arm clinical study. If you agree and are eligible to participate, you will be treated with the Neva VS device.

WHAT TESTS, PROCEDURES, AND DIAGNOSTIC STUDIES WILL BE DONE DURING THIS STUDY?
Most tests are routine, standard of care following aSAH. If you sign this consent form, you allow the results to be shared with the Sponsor of the study and its representatives.

Medical history: the study doctor and/or research team will examine your available medical records and ask you questions about your health, your medical history and hospitalizations including assessments performed when you were originally admitted for your aSAH.

Vital signs: blood pressure, temperature, weight, heart rate, and breathing rate.

Medication review: the study doctor and/or research team will ask you what medications you are taking.

Blood test: you will give a blood sample (about 2-3 tablespoons) for routine blood tests.

Urine test: if you are a woman who can get pregnant, a urine pregnancy test will be performed if it wasn't already performed at hospital admission.

NIH Stroke Scale (NIHSS): a non-invasive examination that measures stroke-related neurological deficits.

Modified Rankin Score (mRS): a non-invasive examination that measures the degree of disability or dependence in daily activities.

Hunt and Hess Scale: a non-invasive examination that measures stroke-related neurological deficits.

Modified Fisher Scale: a non-invasive examination that measures the amount of blood seen from the images of your brain after your aneurysm rupture.

Brain imaging: brain imaging such as a non-contrast head CT scan will be performed to assess for bleeding.

Angiographic imaging: imaging of your brain vessels will be performed for confirmation and location of the vasospasm and to determine access to the blood vessel.

Transcranial Doppler: a non-invasive ultrasound imaging method that measures the velocity of blood flow through your blood vessels in your brain.

***Intervention*:** After applying a local anesthetic (numbing medication), the interventional surgeon will make two small incisions in your groin area and introduce small plastic tubes (called access sheaths) through the incisions. Through the access sheaths, the interventional surgeon can introduce a longer tube (called catheter) to inject dye (contrast medium) and use x-rays (fluoroscopy) to see your blood vessels on a monitor. The interventional surgeon will look at your blood vessels to see if you are a good candidate for the Neva VS procedure. If you qualify, the NeVa VS device is advanced through the tube into your blood vessel to the location of the

vasospasm(s). The device will be temporarily expanded for few minutes and then moved along the blood vessel to other location(s) for temporarily expansion. After all locations are treated, the device and the tubes (catheters and access sheaths) will be removed. The entire procedure should take approximately one hour.

Assessment of adverse events – Assessment of any unpleasant medical experiences, side effects, or discomforts that may happen to you.

Visit # 1: Screening
Screening will involve the following procedures: medical history, Hunt and Hess Grade, modified Fisher Scale, NIHSS, mRS, vital signs, blood test, urine pregnancy test (if applicable), transcranial Doppler, and medication review.

Visit # 2: Intervention/Procedure (Day 0)
After angiographic imaging to confirm your eligibility, the intervention with the Neva VS device and assessment of adverse events will be performed.

Visit # 3 – 24 hours
At this time, vital signs, brain imaging, transcranial Doppler, NIHSS, mRS, and assessment of adverse events will be performed.

Visit # 4 – 21 Days after aSAH or Discharge (whichever occurs first)
At this time, brain imaging, medication review, transcranial Doppler, NIHSS, mRS and assessment of adverse events will be performed.

Visit # 5 – 30 Days
At this time, mRS and assessment of adverse events will be performed.

Additional Treatment for New or Recurring Vasospasm Before Hospital Discharge
If vasospasm recurs or you experience vasospasm in other areas of your brain before you are discharged from the hospital, you may receive additional treatment with the NeVa VS.

HOW LONG WILL I BE IN THIS RESEARCH STUDY?
Your last follow up visit will be approximately 30 days after your last treatment with NeVa VS. After this visit, you will have completed this study.

WHAT DO I HAVE TO DO AS A PARTICIPANT IN THIS STUDY?
Participation in this study requires you to attend all your scheduled visits. During your participation in the study you will be asked to report any unpleasant medical experiences that you may have. You also must not participate in any other clinical trial while participating in this study.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data pertain to a side effect related to the study. If such an event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled and will not affect your access to health care. If you do decide to stop your participation in the study, you should talk to your doctor immediately, so he/she can advise you of any additional tests that may be needed for your safety. Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if he/she determines that it is no longer in your best interest to continue. The Sponsor or regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified and your study doctor will discuss with you other options you may have.

WHAT ARE THE RISKS OF THIS RESEARCH STUDY?

Below is a description of these risks. Your doctor will discuss the risks and procedures with you before you start in the study.

Risks from NeVa VS Intervention

As described above, the interventional surgeon will make two small incisions in your groin area and introduce small plastic tubes through the incisions. These tubes (called access sheaths and catheters) are placed in your blood vessels to establish access for Neva VS procedure. There may be pain or discomfort at the insertion sites and risk of infection. There is also a small risk of nerve damage that may cause pain and/or tingling at the sheath insertion site or down the leg. There is risk of damage to the artery or vein resulting in swelling, bruising, bleeding, or hematoma (collection of blood in the soft tissue) at the insertion site or deeper in the pelvis/abdomen. Bleeding complications may result in decreased blood pressure, increased heart rate, and, in severe cases, need for transfusion. There is some risk that introducing instruments will cause the artery or vein to spasm or narrow (stenosis) and require treatment. There is a risk that a blood clot will form in the blood vessel that requires treatment. Additional treatments for these risks may include, medications, an additional procedure, or in rare cases surgery. When the sheaths and catheters are removed, manual compression is used to stop bleeding which may also cause discomfort or pain. The introduction of devices in the brain blood vessels may cause local injury including brain bleeding and/or strokes. Brain bleeding and/or strokes can cause permanent paralysis and/or loss of sensation in of one or more limbs and/or face as well as speech and/or visual problems, and even coma or death.

Possible risks from the use of X-rays (fluoroscopy) and dye (contrast medium): X-rays (fluoroscopy) will be used during sheath/ catheter placement and to visualize your blood vessels. The total fluoroscopy time and radiation exposure is estimated at several minutes and delivers approximately the same amount of radiation as a regular chest X-ray. Rare but possible effects of

radiation include: alopecia, (hair loss) burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia (cancer). The interventional surgeon will also use dye (contrast medium) to better see your blood vessels during fluoroscopy. Contrast medium may cause a sensation of warmth or occasionally nausea which lasts a few minutes. In rare cases, contrast medium causes a mild reaction such as hives or skin redness. More serious reactions have been known to occur (rarely) including damage to your kidneys, and inflammation (swelling) of the blood vessels, or (very rarely) a life-threatening problem with breathing or blood flow.

Risks from Non-Contrast Head CT scan
There is always a slight chance of cancer from excessive exposure to radiation. However, the benefit of an accurate diagnosis far outweighs the risk.

Women should always inform their physician and x-ray or CT technologist if there is any possibility that they are pregnant. CT scanning is, in general, not recommended for pregnant women unless medically necessary because of potential risk to the baby.

Risks from Blood Tests
You will have routine blood samples taken from a vein in your arm by a needle stick. Risks associated with drawing blood from your arm include slight discomfort and/or bruising. Infection, bleeding, clotting, or fainting are also possible, although unlikely.

Unknown risks
In addition to the risks already described, there may be other discomforts or risks from this study agent and/or procedures that we do not know about. You will be watched for signs and symptoms of any side effects and you should tell your doctor if you do not feel well or experience any unusual symptoms.

In the event of your death, an autopsy will be requested. It would be done to provide additional information about the research. Your family and your "legally authorized representatives" have the right to refuse the autopsy even if you sign this consent form.

ARE THERE BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?
There may be no direct benefit to you by participating in this study. However, it is possible that the Neva VS device diminishes or eliminates the vasospasms in your brain which may result in subjects experiencing less severe ischemic brain injury and less final disability, but there are no guarantees.

Knowledge from this study may help us better understand how to treat people with vasospasm.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?
If additional data regarding potential safety risks become available during the study, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will make arrangements

for your care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form which will explain the new information clearly.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

WILL I NEED TO PAY FOR THE TESTS AND PROCEDURES?
Participation in this study will be of **no cost** to you. All medical exams, urine and blood tests, and study evaluations and procedures that are specifically required for this research study only are provided to you at no cost to you. You will also not need to pay for the NeVa VS device. Vesalio Co., Ltd. pays for this research. However, if taking part in this study leads to procedures or care not included in this study, it may lead to added costs for you or your insurance company.

WILL I BE PAID TO TAKE PART?
You will not receive any payment for taking part in this research study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?
In the event of an injury resulting from your participation in this study, you will be provided with appropriate medical care. However, the costs incurred may, ultimately, be borne by your medical insurance. Further information concerning this and your rights as a research subject can be obtained from [NAME OF PRINCIPAL INVESTIGATOR] or by phone [PHONE NUMBER] or by mail:

[MAILING ADDRESS]

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?
You have the right to refuse to sign this consent. Taking part in this research study does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care from your doctor. If you stop the study, you would still receive medical care for your condition although you would not be able to be treated with the Neva System.

WHAT ABOUT CONFIDENTIALITY?
The personal information obtained about you during the course of this study will remain confidential. When recording the results of the study you will be referred to only by a unique subject identifier code number and your initials. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records.

Your records may be reviewed in order to meet Federal Food and Drug Administration (US FDA) regulations, or other national and/or local health regulatory authorities. Your records may be copied by, or for these groups. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Copies of the study records that do not include your name but may be traced back to you may also be given to the groups listed below. The Sponsor may send a copy of the records to the FDA or other regulatory agencies.

By agreeing to participate in this research study, you consent to give representatives of the following entities access to your research-related medical records to ensure the proper conduct of the research and to verify the accuracy of the collected data.

Clinical monitors, auditors, IRB members, and regulatory authorities will be granted access to your original medical records for verification of clinical trial procedures and/or data, without violating your confidentiality, to the extent permitted by the applicable laws and regulations.

Reviewers for the study may include the Sponsor (Vesalio Co., Ltd.), or its representatives such as members of the Data Safety Monitoring Board, the Contract Research Organization identified as BioMDG, Inc., and the IRB or other Research Committee(s) that approve and oversee research in the hospitals and clinics. Additionally, representatives of national regulatory authorities (for example the Food and Drug Administration in the USA), representatives of the central laboratory facilities appointed by the Sponsor responsible for analyzing the blood tests, and other representatives as designated by the Sponsor who will have a role in the handling and analysis of the study data or in trial operations.

Complete confidentiality cannot be promised because information needs to be shared as described. However, information will be collected and shared following professional standards of confidentiality.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT WILL HAPPEN TO THE RESULTS OF THIS STUDY?
The results of this research study will be used to support an application to regulatory agencies that approve medical devices. In addition, the results may be used in scientific publications or presented at medical meetings. Your identity as a participant will not be revealed.

WHO HAS REVIEWED THIS STUDY?
The study has been reviewed by the FDA and an IRB (research ethics committee).

WHO CAN ANSWER MY QUESTIONS?

If you have any questions, concerns, or complaints about this research study, you may call the study site. If you think you have an injury or illness from the study agent, contact the study doctor listed on the first page of the consent form.

You should contact the study doctor first if you have questions, complaints, or concerns about the study.

Please call [Name] IRB at [Phone number] if:

- You want to talk to someone other than the study doctor or study staff.
- You have a hard time reaching the study doctor or study staff.
- You have questions about your rights as a research subject.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
If you choose not to take part in this study, other treatment for vasospasm such as endovascular therapy with vasodilators and angioplasty balloons is available to you. You do not have to take part in this study to receive treatment for your condition.

STATEMENT OF CONSENT

I confirm that I have read and understand this consent form. I confirm that the purpose of this study, procedures to be followed, and risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have decided of my own free will to agree to take part in this study.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

I understand that sections of any or all of my medical records may be reviewed by representatives of the Sponsor, Vesalio, its subcontractors, or by regulatory authorities where it is relevant to my taking part in this research. I understand that I will not be referred to by name in any report concerning the study. I agree to disclosure of such records and any results to the regulatory authorities. I understand that I will be provided clinically-appropriate medical care and that I have access to my doctor in case of any injury or deterioration in my health or well-being caused directly by my participation in this study.

Printed Name of Participating Subject		
Signature of Participating Subject	Date	Time
Printed Name of Legal Authorized Representative (if subject in unable to sign)		
Signature of Legal Authorized Representative	Date	Time
Signature of Physician or his/her Representative Obtaining Consent	Date	Time

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) AUTHORIZATION

Federal regulations give you certain rights related to your health information. These include the right to know who will receive the information and how it will be used. The study doctor must obtain your authorization (permission) to use or release any health information that might identify you.

What information may be used and shared?
The study doctor and study staff will use and share your health information as part of this research study. This may include your name, address, telephone number or other facts that could identify the health information as yours.
Examples of the information that may be used are:

- Medical records (from any doctor, hospital or other healthcare provider)
- Information created or collected during the research. This could include your medical history, and dates or results from any physical exams, laboratory tests or other tests.

Who will receive information about you?
The study doctor and study staff will share your personal health information with:

- the sponsor, including persons or companies working for or with the sponsor
- [Name] Independent Review Board
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- other regulatory agencies

Why will this information be used and/or given to others?
The sponsor and the groups above will use your health information:

- to complete this research
- to evaluate the results of the study
- to check that the study is being done properly
- to obtain marketing approval for new products resulting from this research

Is my health information protected after it has been given to others?
Your health information may be further shared by the groups above. If shared by them, the information will no longer be covered by this Authorization. These groups are committed to keeping your health information confidential.

What if I decide not to allow the use of my health information?
You do not have to sign this form. If you do not sign this form, you cannot take part in this research study.

May I withdraw or revoke (cancel) my permission?

YES. You may withdraw your permission to use and disclose your health information at any time. You can do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in the research study.

What happens if I want to withdraw my authorization?
Information that has already been gathered may still be used and given to others. If you withdraw your permission, no new health information will be gathered unless you have a side effect related to the study. If you withdraw from the study but do not withdraw your Authorization, new health information may be collected until this study ends.

Will my authorization expire?
If you do not withdraw this Authorization in writing, it will remain in effect.

This Authorization [does not have an expiration date. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely.] ***OR [will expire December 31, 2060, unless you withdraw it in writing before then.] (FOR CA, WA, WI, IN SITES)***

The study doctor will keep this Authorization for at least 6 years.

May I review or copy the information obtained or created about me?
YES. You have the right to review and copy your health information. However, your access to this information may be delayed until the study is complete.

Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

AUTHORIZATION
By signing this form, I allow the use or disclosure of my health information. I will receive a signed and dated copy of this Authorization.

Printed Name of Subject

Signature of Subject **Date**

Printed Name of Legal Authorized Representative (if subject is unable to sign)

Signature of Legal Authorized Representative **Date**

Appendix 3. Neva VS Device – Draft Instructions for Use

Vesalio NeVa VS System : Instructions for Use

CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.

Caution: This device is restricted to use by or on the order of a physician.

As with any medical treatment, it is the responsibility of the surgeon/physician to use his or her judgment in utilizing the procedures best suited to the needs of the patient. Only physicians trained in neuro-interventional procedures should utilize the Vesalio NeVa VS (Vasospasm) System.

The Vesalio VS System contains (1) NeVa vessel dilation device.

INDICATION FOR USE

The NeVa VS System is indicated for the treatment of cerebral ischemia resulting from symptomatic vasospasm following subarachnoid hemorrhage (aSAH), secured by either surgical or endovascular intervention for patients who have failed maximal medical management. The NeVa VS System is temporarily deployed within the vasospastic vessel segment where the intrinsic outward radial force of the nitinol tip expands the vessel.

The Vesalio NeVa VS System is indicated for:

- Endovascular temporary use in patients with acute cerebral ischemia related to aSAH induced cerebral vasospasm
- Endovascular temporary use to increase vessel diameter and blood flow in patients who are experiencing symptoms of acute ischemia related to aSAH associated vasospasm.

CAUTION: Evaluate the risks associated with acute endovascular vasospasm therapy (see complications below) and the possible benefits of intravascular vessel dilation prior to use of the Vesalio NeVa VS System. Take all necessary precautions to limit X-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

CONTRAINDICATIONS

- Presence of an unsecured, ruptured intracranial aneurysm
- Patient allergy to NeVa VS components (nickel).
- Patients with suspected or known allergies to contrast media
- Pregnancy
- Excessive vessel tortuosity that prevents the placement of the device
- Known hemorrhagic diathesis, coagulation factor deficiency or oral anticoagulant therapy with INR>1.7
- Patient has baseline platelets <30,000
- Evidence of rapidly improving neurological signs of stroke
- Large territory completed cerebral infarction, edema with mass effect and intra-parenchymal hemorrhage in vascular territory to be treated

WARNINGS AND PRECAUTIONS

- The Vesalio NeVa VS System should only be used by physicians who have received appropriate training in cerebral endovascular techniques.
- The Vesalio NeVa VS System family of products, as noted in the Recommended Sizing Guideline Table, is designed for use in vessels with a pre-vasospasm diameter ≥ 2.0mm and ≤ 4.0mm in diameter. Use of the device in vessel diameters outside the recommendation can produce vessel injury.
- The NeVa VS should only be used with the Trevo Pro 18 Microcatheter
- The device is provided STERILE for single patient use only. Reusing the device could result in compromised device performance, cross-infection and other safety related hazards.
- Store in a cool, dry place.
- Do not re-sterilize. After use, dispose in accordance with hospital, administrative and/or local government policy.
- Use the device prior to the 'Use By Date' date printed on the package.
- Carefully inspect the sterile package and device prior to use to verify that neither has been damaged during shipment. Do not use kinked or damaged components.
- The Vesalio NeVa VS System has not been shown to be MRI compatible.
- Tighten the Rotating Hemostasis Valves sufficiently to create an adequate hemostasis seal without crushing the introducer sheath and Vesalio NeVa VS System shaft. Inadequately tightening the Rotating Hemostasis Valves my lead to premature deployment of the device.
- After deployment, the distal tip of the device may foreshorten.

COMPLICATIONS

Possible complications of the use of the Vesalio NeVa VS System include but are not limited to:

- Perforation or dissection of the vessel
- Air embolism
- Arterial perforation with guidewire
- Subarachnoid/interventricular hemorrhage due to vessel perforation from guidewire placement or device microcatheter placement.
- Vascular spasm or vascular occlusion
- Neurologic deterioration including stroke and death
- Distal embolization including to a previously uninvolved territory
- Pseudo aneurysm formation
- Device(s) deformation, collapse, fracture or malfunction
- Displacement of coils or clips used to secure an aneurysm

Complications of routine endovascular revascularization include:

- Cerebral ischemia
- Coagulopathy
- Confusion
- Death
- Embolic stroke
- Hematoma, pain, and/or infection at access site
- Intracerebral/intracranial hemorrhage
- Post-procedure bleeding
- Pseudoaneurysm formation
- Renal failure
- Vessel thrombosis

PROCEDURE

The **Vesalio NeVa VS System** is delivered endovascularly under fluoroscopic guidance in a manner consistent with other neurovascular catheter-based devices.

Antiplatelet and anticoagulation regimen used for interventional intracranial procedures is to be performed at the discretion of the treating physician.

Procedure Steps:

Angiographic Assessment of Vessel and Device Selection

1. Using angiography, determine the location of the vasospastic vessel segment
2. Review the patient's pre-vasospasm digital subtraction angiogram or equivalent vascular study (CT angiogram) to confirm that the segment to be treated has a diameter of at least 2.0mm prior to deployment. Recommended vessel diameter for the fully expanded portion of NeVa VS is a pre-vasospasm diameter of 2mm. The distal tapered portion and marker coil extend 10mm beyond the fully expanded segment. **No more than 6 device interventions per vessel should be attempted.**

Table 1: Vesalio NeVa VS System

Product Name Numbers and Recommend Sizing Guidelines

Product Number	Product Name	Labeled Device Diameter (mm)	Labeled Device Length (mm)	Self Expanded Device Diameter (mm)	Recommended Pre-vasospasm Vessel Diameter (mm)	Pusher Length	Introducer Microcatheter	Max. Guidewire Diameter
30050V-VS	NeVa VS	4.0	22	4.0	≥ 2.0 and ≤ 4.0	180cm	Trevo Pro 18	NA

Vesalio NeVa VS System Preparation and Procedure

<u>Preparation</u>

1. Administer anti-coagulation and anti-platelet medications per standard institutional guidelines.
2. Aided by angiographic radiography and reviewing the pre-vasospasm vascular imaging determine the location and size of the area to be revascularized.
3. To achieve optimal performance of the Vesalio NeVa VS System and to reduce the risk of thromboembolic complications, maintain continuous flushing action between a) the femoral arterial sheath and the guide catheter, b) the microcatheter and the guide catheter and c) the microcatheter and the push wire and the Vesalio NeVa VS System. Check all connections to make sure that during the continuous flush that no air enters the guide catheter or the microcatheter.
4. Position a suitable guide catheter employing a standard method. The guide catheter should be appropriately sized to allow for angiography around the microcatheter. Connect a RHV to the fitting of the guide catheter, and then connect a tube to the continuous flush.
5. With the aid of Table 1, select a microcatheter suitable for advancing the Vesalio NeVa VS System.
6. Connect a second RHV to the fitting of the microcatheter and then connect a tube to the continuous flush.
7. Set the flush rate per standard institutional guidelines.
8. With the aid of a suitable guide wire, advance the microcatheter until the end of the microcatheter is positioned as distal as possible within the treatable segment of the vasospastic vessel. The treatable segment is determined by reviewing the pre-vasospasm angiographic imaging to ensure that the segment is at least 2.0mm in diameter. Remove the guidewire and perform a microcatheter angiogram to ensure proper intra-vascular positioning of the microcatheter prior to deployment.

<u>Delivering the Vesalio NeVa VS System</u>

9. Insert the distal end of the introducer sheath partially into the RHV connected to the microcatheter. Tighten the RHV and verify that fluid exits the proximal end of the introducer sheath.
10. Loosen the RHV and advance the introducer sheath until it is firmly seated in the hub of the microcatheter. Tighten the RHV around the introducer sheath to prevent back flow of blood, but not so tight as to damage the Vesalio NeVa VS System during its introduction into the microcatheter. Confirm that there are no air bubbles trapped anywhere in the system.
11. Transfer the Vesalio NeVa VS System into the microcatheter by advancing the push wire in a smooth, continuous manner. Once the flexible portion of the push wire has entered the microcatheter shaft, loosen the RHV and remove the introducer sheath over the proximal end of the push wire. Once completed, tighten the RHV around the push wire. Leaving the introducer sheath in place will interrupt normal infusion of flushing solution and allow back flow of blood into the microcatheter.
12. Visually verify that the flushing solution is infusing normally. Once confirmed, loosen the RHV to advance the push wire.
13. With the aid of fluoroscopic monitoring, carefully advance the Vesalio NeVa VS System until its distal marker lines up at the end of the microcatheter.

WARNING: IF EXCESSIVE RESISTANCE IS ENCOUNTERED DURING THE DELIVERY OF THE VESALIO NEVA VS SYSTEM, DISCONTINUE THE DELIVERY AND IDENTIFY THE CAUSE OF THE RESISTANCE. ADVANCEMENT OF THE VESALIO NEVA VS SYSTEM AGAINST RESISTANCE MAY RESULT IN DEVICE DAMAGE AND/OR PATIENT INJURY.

<u>Deploying the Vesalio NeVa VS System</u>

14. Loosen the RHV around the microcatheter. To deploy the Vesalio NeVa VS System, fix the pusher wire to maintain the position of the device while carefully withdrawing the microcatheter in the proximal direction. Do not advance the NeVa VS System beyond the distal tip of the microcatheter, doing so risks damage to the vessel and/or the device.
15. Retract the microcatheter until it is proximal to the proximal marker of the Vesalio NeVa VS System. Tighten the RHV to prevent any movement of the push wire.
16. Allow the NeVa VS to remain in place for up to 10 minutes, frequent spot fluoroscopy and angiographic imaging is encouraged to evaluate device expansion and to evaluate for any complications such as thrombus formation.
17. Do not advance or withdraw the device against resistance or significant vasospasm as moving or torqueing of the device against resistance or significant vasospasm may result in damage to the vessel or device
18. After complete expansion or 10 minutes, re-capture the NeVa VS System into the microcatheter using the following steps: Loosen the RHV around the microcatheter and around the push wire. With the aid of fluoroscopic monitoring, hold the push wire firmly in its position to prevent the Vesalio NeVa VS System from moving. Carefully re-sheath the Vesalio NeVa VS System by advancing the microcatheter over the Vesalio NeVa VS System until the distal markers of the Vesalio NeVa VS System line up at the end of the microcatheter.
19. Once re-captured in the microcatheter, the catheter can be withdrawn to a more proximal segment and the device re-deployed to treat proximal vasospasm following steps 15-17 above.

WARNING: IF EXCESSIVE RESISTANCE IS ENCOUNTERED DURING MICROCATHETER RE-CAPTURE OF THE VESALIO NEVA VS SYSTEM, DISCONTINUE THE RE-CAPTURE AND IDENTIFY THE CAUSE OF THE RESISTANCE. IF THERE IS CONTINUED RESISTANCE, WITHDRAW THE MICROCATHETER AND NEVA VS SYSTEM TOGETHER AND RE-CAPTURE INTO THE GUIDE CATHETER. DO NOT PERFORM MORE THAN SIX DEPLOYMENTS AND MICROCATHETER RE-SHEATHING ATTEMPTS USING A SINGLE VESALIO NEVA VS SYSTEM.

20. After the last deployment, re-capture the device into the microcatheter following the steps above and withdraw the microcatheter and NeVa VS System through the guide catheter. Open the guide catheter RHV to allow the microcatheter and the Vesalio NeVa VS System to exit without resistance. Use care to prevent air from entering the system.
21. If additional vessel dilation attempts are desired with:
    a new Vesalio NeVa VS System, then repeat the steps described above starting with the "Preparation" section.

the same Vesalio NeVa VS System, then:

a. Clean the device with saline solution. **Do not use solvents or autoclave.**

b. Carefully inspect the device for damage. If there is any damage, do not use the device and use a new Vesalio NeVa VS System for subsequent vasodilation attempts following the steps described above starting with the "Preparation" section. Use of a damaged device could result in additional device damage or patient injury.

WARNING: DO NOT USE EACH VESALIO NEVA VS SYSTEM FOR MORE THAN SIX DEPLOYMENTS AND MICROCATHETER RETRIEVALS.

HOW SUPPLIED

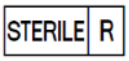
Each **Vesalio NeVa VS System** contains one device positioned in an introducer sheath. All are supplied STERILE (Gamma) and **FOR SINGLE USE ONLY**. All components should be handled carefully to avoid damaging the device.

STORAGE AND HANDLING

Handle with care. Packages should be stored in a manner that protects the integrity of the package; packages should be stored at a controlled room temperature in a dry place.

WARRANTY AND LIMITATION OF WARRANTY

Vesalio LLC warrants that reasonable care was used in the design and manufacture of this product. Because **Vesalio LLC** has no control over the conditions of use, patient selection or handling of the device after it leaves its possession, **Vesalio LLC** does not warrant either a good effect or against an ill effect following its use. **Vesalio LLC.** shall not be directly or indirectly responsible for any incidental or consequential loss, damage or expenses directly or indirectly arising from the use of this product. **Vesalio LLC** sole responsibility in the event **Vesalio LLC** determines the product was defective when shipped by **Vesalio LLC,** shall be the replacement of the product. This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether expressed or implied by operation of law or otherwise, including but not limited to any implied warranties of merchantability or fitness for use.

Symbols Glossary			
	Lot number		Do not reuse
	Model number		Keep dry
	Sterile (Gamma Radiation)		Manufacturer
	Use -by date		Do Not use if package is damaged
	Warning		Read the documentation
21MC	For use only with Trevo Pro 18 microcatheter	**Rx** Only	Prescription
	Do not re-sterilize		

Manufacturer:
Vesalio LLC
105 North Pointe Drive
Lake Forest, CA 92630 USA
Telephone: +615-206-7788

Patents www.vesalio.com/patent

Appendix 4. NIH Stroke Scale

Date of Exam: Time of exam: ___ ____ : ___ ___ am / pm

Person Administering Scale:_____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____	
	5a. Left Arm	_____
	5b. Right Arm	_____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____	
	6a. Left Leg	_____
	6b. Right Leg	_____

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

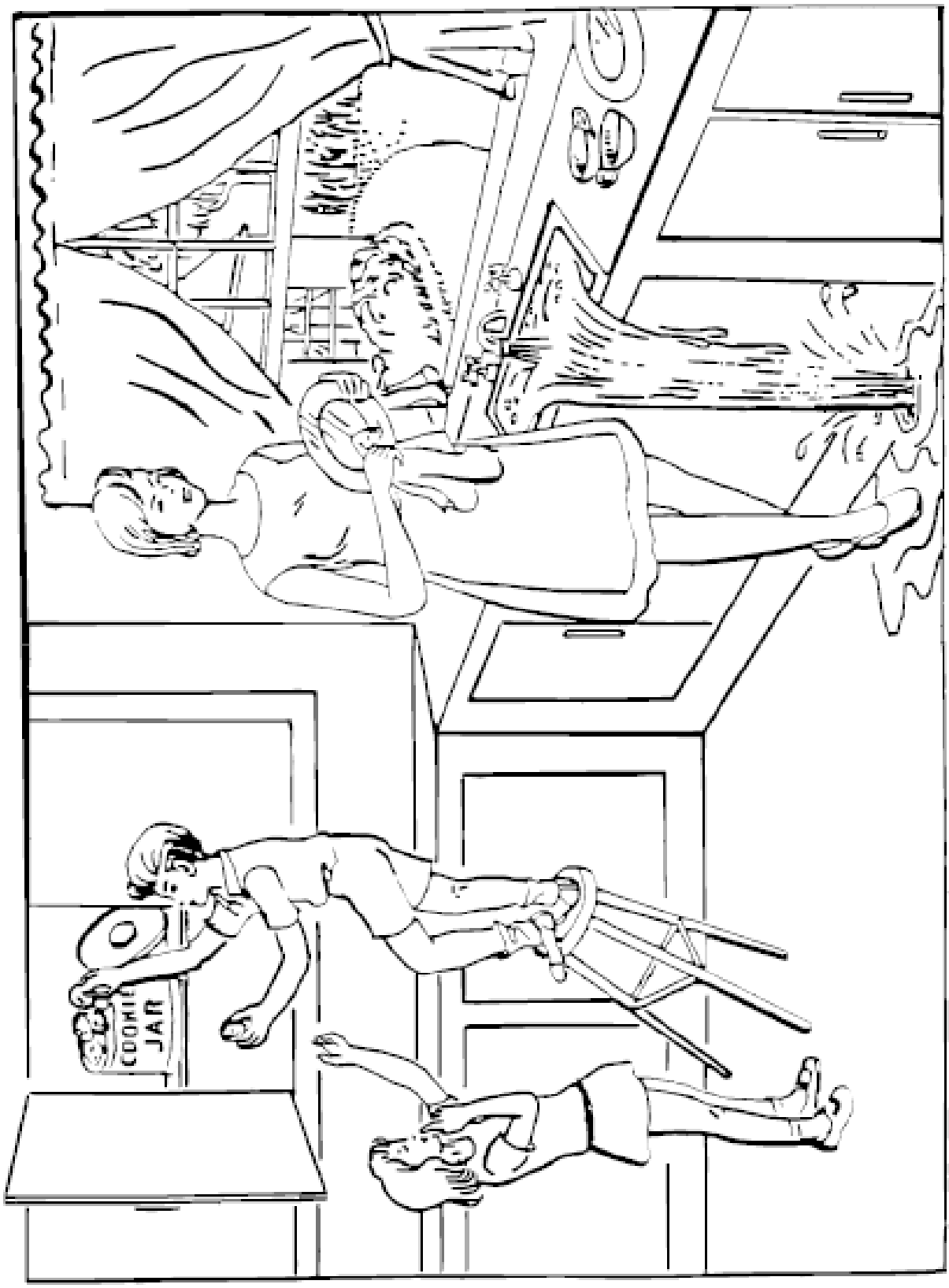
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

0 = **No abnormality.**

1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.

_____


COOKIE
JAR

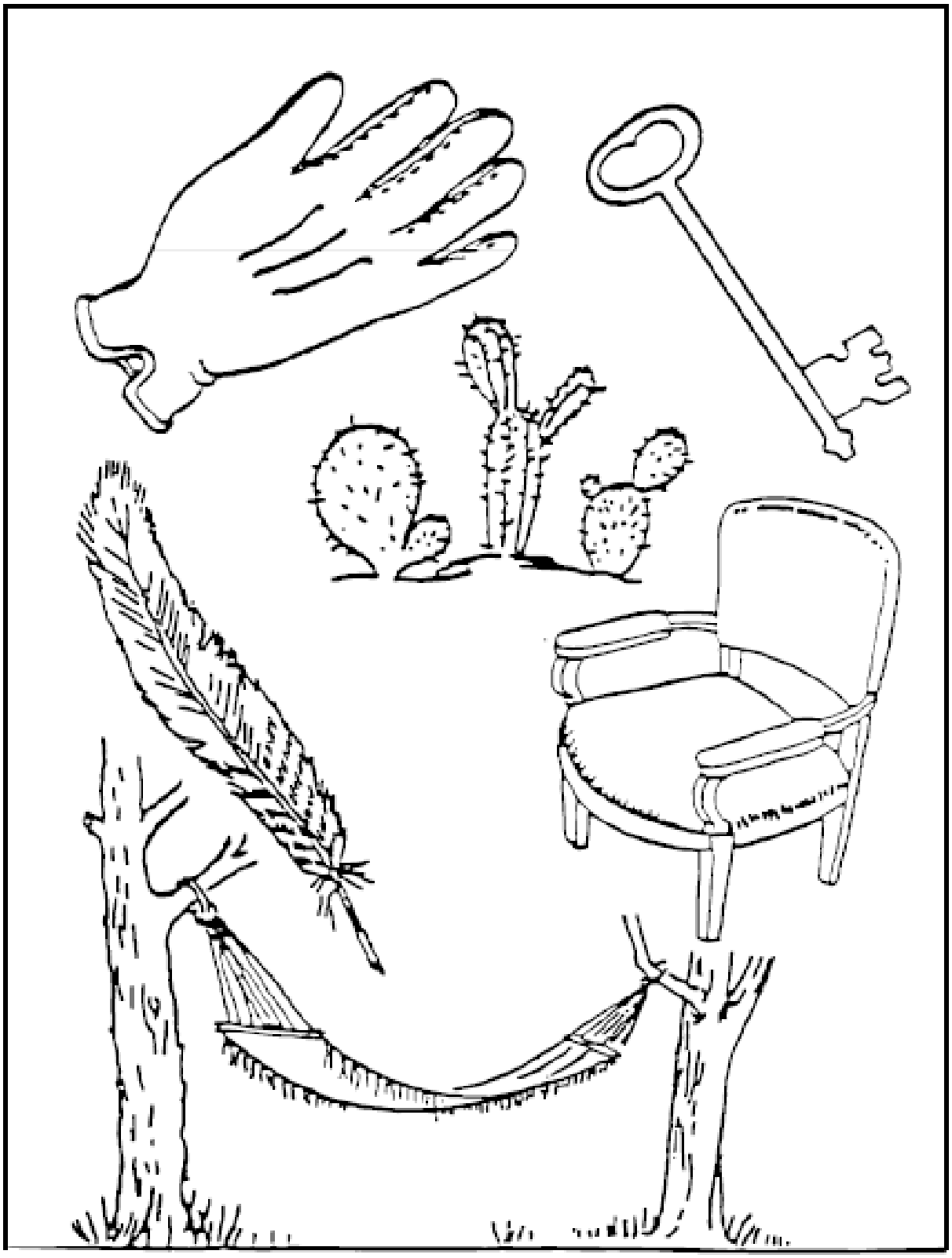
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix 5. Investigator's Qualifications and Responsibilities

The investigators have the following responsibilities:

1. Subject Selection

The investigator is responsible for assuring that all subjects entering the study conform to the subject selection criteria.

2. Informed Consent

The investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with the prospective subject/legal representative prior to their enrollment in the study. The investigator is responsible for obtaining written Informed Consent in compliance with 21 CFR 50 for each subject or his/her legal representative, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the subject's medical record.

3. Institutional Review Board (IRB) Approval

The investigator must obtain approval for his participation in this protocol from the IRB for the institution at which the procedure will be performed, prior to entering any subjects in the study. The Informed Consent document to be used will also be submitted by the Investigator to the IRB for approval prior to initiation of the study. Assurance that the IRB approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor/Designee prior to initiation of the study.

4. Subject Evaluations and Data Reporting

The investigator, or trained designee, is responsible for performing the subject assessments as described in the study protocol. Information generated by these evaluations will be recorded on the CRFs provided by the Sponsor/Designee or entered into the electronic data capture system (EDC) with access provided by the Sponsor/Designee.

Following each subject visit, the CRFs will be completed in a timely manner, e.g., within 48 hours. Original reports from the subject assessments (source documents) will be retained as part of the subject's study file.

Investigator(s) will not deviate from the study protocol without prior approval of the Sponsor/Designee unless protection of the health, safety or welfare of study subjects requires prompt action.

5. Record Retention

In accordance with Commission Directive 2005/28/EC, the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion.

The investigator shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the investigator.

Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

6. Investigational Material Accountability

The investigator must maintain accurate records of the receipt of investigational material shipped by the Sponsor/Designee, including the date and lot numbers received. In addition, accurate records must be kept on the amount and date that investigational material, by lot number, was used or returned for each subject in the trial. The investigator must assure that study supplies be used only in subjects enrolled in the study and under the direct supervision of the investigator or co-investigators.

Records of all investigational supplies received, used and returned must be kept by the principal investigator or his/her designee. All unused investigational supplies will be returned to the Sponsor/Designee as soon as practical upon completion of enrollment. Investigational material accounting procedures must be completed before the study is considered terminated.

Appendix 6. Sponsor's Commitments

Vesalio is committed to:

1. Complying with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.

2. Protecting the rights, health, safety, and welfare of study subjects.

3. Informing the clinical investigators of any new information about the study, which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.

4. Providing the clinical investigators with the study protocol, and a full set of / access to CRFs on which to document the study evaluation variables for each subject entered into the study.

5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.

6. Ensuring equity of consideration among all investigators in multicenter studies in all matters of publications, meeting presentations, etc.

7. Certifying that IRB approval of the protocol and completion of the Investigator's Agreement will occur prior to treatment at any investigational site.